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The Clinical Problem of Agammaglobulinemia

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In 1952 Bruton[1] described a new disease featured by recurrent bacterial infection. Because of the absence of gamma globulin in the serum, he used the term agammaglobulinemia to define this disease. Subsequent studies have shown that isolated deficiency of gamma globulin may occur as the essential feature of at least two separate clinical syndromes.

The patients initially described by Bruton[1] and later by Bruton et al.[2] and Janeway et al.[3] were all male children each having a history of bacterial infection dating back to the last half of the first year of life. Subsequent evidence has indicated that this disease may occur in male siblings and male cousins related through the maternal side of the family.[3-5] Historical evidence of early death from infection among male members of the mother's family also has been obtained. These observations suggest strongly that one form of agammaglobulinemia is an inborn error of metabolism transmitted as a sex-linked recessive trait.

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In addition to and apparently distinct from this form of the disease is a similar clinical disorder which occurs in adults. Typically, patients with this form of agammaglobulinemia are well until a certain time in their lives when they begin to have frequent severe bacterial infections. Following the apparent onset of their illness, these patients, like the children with the congenital form of agammaglobu-

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linemia, are plagued with one severe bacterial infection after another. Unlike the congenital form of the disease which seems to be limited to boys, acquired agammaglobulinemia may begin in either sex at any age. The cardinal features of both congenital and acquired agammaglobulinemia are increased susceptibility to bacterial infection, absence of gamma globulin in the blood and tissues, absence of antibodies in the blood and tissues and failure of antibody production in response to antigenic stimuli.

Deficiency of serum gamma globulin may occur as part of other disease syndromes. For example, in some patients[6-8] there is a general failure of protein fabrication which includes the gamma fraction. Clinically these patients suffer primarily from a nonproteinuric, generalized edema. Occasionally even in this syndrome gamma globulin levels get down sufficiently low so that recurrent infections may be a problem.[6] In nephrotic patients, loss of gamma globulin as well as albumin in the urine[9] may result in extreme hypoalbuminemia and hypogammaglobulinemia. It is postulated that the latter disturbance is responsible in some degree for the well-known susceptibility of nephrotic patients to pneumococcal and other bacterial infections. In a few patients suffering from prolonged severe nutritional deprivation, hypogammaglobulinemia may result.[10] Occasionally, excessive destruction of serum proteins may result in hypogammaglobulinemia as well as in general hypoproteinemia.[11,12]

Of perhaps special clinical significance are the instances of transient hypogammaglobulinemia of infancy. Normally, newborn infants possess high levels of gamma globulin, most or all of which is derived from the mother.[13-17] Shortly after birth the gamma globulin begins to fall in both relative and absolute concentration until low levels are reached between one and three months after birth.[14,16,18,19] Then begins a gradual increase in the gamma globulin concentration until levels within the normal range for adults are attained between two and six years of age.[8,16] In some babies the decline of gamma globulin level is excessive, probably because of a delay in the assumption of immunologic responsibility on the part of the child, and the transient hypogammaglobulinemia of infancy may result. Kelley[20] recently has studied such a case. Spain et al.[21] have postulated that the phenomenon of crib death occurring in babies between one and four months old might be due to the low levels of gamma globulin which may be encountered at this age. They found low gamma globulin concentration in each of three infants dying a crib death from pneumonia. Ulstrom[22] recently studied four infants in whom transient hypogammaglobulinemia of infancy was associated with anemia.

Finally, in multiple myeloma the production of abnormal gamma globulins—which on electrophoretic analysis may migrate as slow gamma, fast gamma, M protein, B globulins, fibrinogen or even as alpha globulins—seems to dissipate capacity to form normal gamma globulin.[23] In such patients, who may be agammaglobulinemic with respect to normal gamma globulin, antibody production is usually inadequate[24,25] and susceptibility to bacterial infection the rule.

The magnitude of the clinical problem posed by agammaglobulinemia is not clear. The rate at which cases are being discovered and reported indicates that the acquired form and the congenital disease occur with about equal frequency. Both are uncommon but neither is rare. At present, reports of 49 cases of agammaglobulinemia may be found in the literature.

One of the principal concerns of physicians at this time is the early recognition of both the congenital and acquired forms of agammaglobulinemia. In this paper an effort will be made to describe the disease syndrome, point out certain clinical features which might suggest this diagnosis to the family physician, and describe simple laboratory screening tests which may aid him in making a presumptive diagnosis. Our discussion is based on analysis of 49 cases reported in the literature, 30 of which have been of the congenital variety and 19 of which apparently represent the acquired disease. Eight of these cases have been extensively studied in our laboratories and in our own clinic.

Pulmonary Manifestations

Perhaps the outstanding clinical feature and consequently the one which should be mentioned first is the pulmonary manifestations of this disease. In all cases reviewed, pulmonary infections were a striking feature. These manifestations included recurrent bronchitis, pneumonitis, bronchopneumonia and lobar pneumonia. In 11 of the 43 cases analyzed, pulmonary complications were recorded—e.g., bronchiectasis, pleural effusion, empyema and pulmonary fibrosis. The frequency with which severe pulmonary disease occurred was sufficient to warrant the conclusion that pulmonary infection represents a clinical *sine qua non* of the agammaglobulinemia syndrome.

The knowledge that recurrent lower respiratory disease is a characteristic manifestation of agammaglobulinemia should be a significant diagnostic aid to the family physician. In these infections the ordinary pyogenic pathogens play a dominant role. The infections usually are due to pneumococci, streptococci, staphylococci or *Hemophilus*. Because of the dramatic relief often produced by replacement gamma globulin and prophylactic antibiotic therapy, any adult or child having recurrent episodes of pneumonia, pneumonitis or bronchitis deserves a study for the possible existence of agammaglobulinemia.

Bronchiectasis in Agammaglobulinemia

Particularly threatening among the pulmonary diseases observed in patients with agammaglobulinemia has been bronchiectasis. Although it has been noted among both the children with the congenital hereditary form of the disease and the adults with the acquired disease, it seems to be more frequent in the latter.[26] For this reason it has been proposed that an agammaglobulinemia-bronchiectasis syndrome exists in adults. From the information available to date it seems that bronchiectasis probably is secondary to the many repeated attacks of pneumonia and purulent pneumonitis occurring in these patients. Although studies indicate the majority of patients develop bronchiectasis in the absence of recognizable gamma globulin disturbances,[27] it would seem prudent at the present state of our knowledge to rule out agammaglobulinemia in all patients with bronchiectasis. Using this case-finding method a significant number of unsuspected cases of agammaglobulinemia probably would be discovered.

The knowledge that bronchiectasis may occur as a complication of agammaglobulinemia and that it probably is secondary to the frequent pyogenic lower respiratory infection in this syndrome makes it urgent to diagnose agammaglobulinemia as early as possible. Early recognition and prompt institution of prophylactic therapy might serve to prevent the development of permanent complications based on the destruction of the pulmonary parenchyma by bacterial invasion.

Other Bacterial Infections

Although pulmonary disease is very frequent and consequently of central importance in agammaglobulinemia, other bacterial infections may have equal significance. These patients often have recurrent meningitis, severe destructive pyogenic skin infections, septicemia, recurrent otitis media, persistent or recurrent purulent sinusitis, septic arthritis, bacterial intestinal infection and urinary tract infections. In some of the reported cases meningitis has been observed on four or five different occasions. Meningeal infections most frequently have been due to pneumococci, but infections with meningococci, *Hemophilus* and streptococci also have been observed.

In the other infections, as in the pulmonary and meningeal diseases, the purulent pathogenic bacteria ordinarily have been the invading microorganisms. On at least three occasions in our patients, however, infections due to gram-negative bacteria have been a major problem. One of the children with congenital agammaglobulinemia suffered from recurrent urinary tract infection due to a species of *Proteus*. Another child had generalized respiratory disease and chronic otitis media due to infection with *Pseudomonas* bacilli. The latter infection was recalcitrant to treatment and the offending microorganism was resistant

in vitro to all antibiotics save CHLOROMYCETIN®. Prompt clinical and bacteriologic response was obtained when Chloromycetin was administered. On one occasion one of the adults with acquired agammaglobulinemia developed septicemia due to a *Proteus* invasion secondary to infection of a surgical wound. It would thus appear that although most of the infections occurring in agammaglobulinemic patients are due to pneumococci, streptococci, staphylococci or *Hemophilus*, the vulnerability is not limited to diseases produced by these organisms but extends to the less invasive gram-negative bacteria as well.

Virus Infections in Agammaglobulinemia

One of the curious paradoxes turned up by study of the patients with agammaglobulinemia is their apparent ability to deal successfully with virus infections.

As first mentioned by Janeway et al.[3] and later observed in our cases,[28] both children and adults with agammaglobulinemia seem to handle at least some virus infections well. For example, these patients may develop rubeola, chickenpox, mumps, infections with common respiratory viruses, and even polio which they express in the usual way. The clinical symptomatology does not differ from that of the immunologically normal person and clinical recovery ensues at the usual time. Even more striking is the observation that subsequent reexposure to virus infection indicates that these patients become resistant to invasion and like normal persons do not develop the illness again on re-exposure.

The observations of Janeway[3] on the response to vaccination have been most notable. He vaccinated six children with congenital agammaglobulinemia with resultant typical reaction. Subsequent revaccination, as in the normal, resulted in accelerated reaction.

Because Keidan et al.,[29] Kempe[30] and Kozinn et al.[31] observed the development of vaccinia gangraenosum following vaccination in patients with hypogammaglobulinemia, we have not vaccinated our cases of agammaglobulinemia. However, in five of our patients successful vaccination without untoward reaction had been carried out previously by the family physician. According to the history the reactions obtained were normal in every way. In one case, repeated attempts to vaccinate the child were unsuccessful. It is our tentative conclusion that the agammaglobulinemic patients who have developed progressive vaccinia represent the transient hypogammaglobulinemia of infancy rather than true congenital agammaglobulinemia of the sex-linked type. In these babies, defense mechanisms other than those represented by the production of circulating antibody and gamma globulin may be involved.

No satisfactory explanation is available to resolve the dilemma posed by these observations but several possibilities may be offered. First, this apparent paradox may be the expression of a quantitative difference in the requirement for immunologic protection between virus and bacterial disease. Since careful immunochemical studies have shown that all so-called agammaglobulinemia patients possess a minute amount of gamma globulin in their serums, it may be that in this small supply there is sufficient antiviral antibody to provide protection against virus invasion. Support for this concept is the observation that extremely small amounts of gamma globulin administered parenterally protect against certain virus infections, e.g., measles.

Another possibility, namely, that the immunologic failure demonstrated when bacterial antigens are submitted to the agammaglobulinemic patient does not extend to virus antigens, has been rejected by data already reported from our laboratory.[28] Injection of the most potent virus antigens available did not result in antibody production in agammaglobulinemic patients even when maximal advantage was taken of the recall or anamnestic reaction. In one of our cases, a child with congenital agammaglobulinemia, injection of polio virus antigen on five different occasions did not result in a detectable antibody response. These observations must be interpreted as indicating that in patients with both congenital and acquired agammaglobulinemia the immunologic handicap extends to both virus and bacterial antigens.

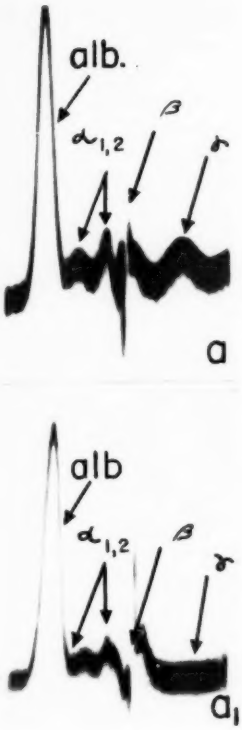

FIGURE 1. Free electrophoretic pattern of a normal child (a) and that of a child with agammaglobulinemia (a_1). The complete absence of gamma globulin in a serum with normal concentration of the other protein constituents is diagnostic of this disease.

Still a third possibility is that some form of local immunity or adjustment within the cells themselves plays a more important role in defense against virus infection than it does in adaptation to bacterial infections. If this were so it would account for recurrences of bacterial disease and resistance to recurrences of virus infection. However, the basis for the difference in susceptibility to virus and bacterial disease in patients with agammaglobulinemia has not yet been explained and it remains a challenge for the future.

That the capacity of these patients to resist virus infections may not extend to all viruses is suggested by observations already available. In one of our cases, that of a 58 year old man, a disease developed which appeared to be viral hepatitis.[32] This illness progressed relentlessly to a fatal termination in a two week period taking the clinical course typical of acute yellow atrophy of the liver.

One of Janeway's[33] patients developed a dis-

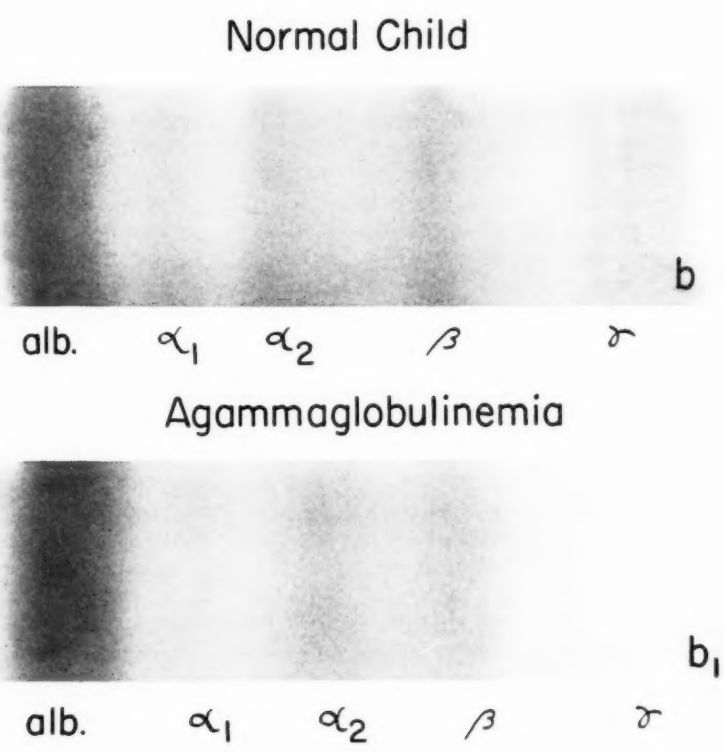

FIGURE 2. Comparison of paper electrophoretic patterns of serum from normal child (b) and child with agammaglobulinemia (b_1). Note the complete absence of gamma globulin in the lower pattern.

ease diagnosed clinically as virus hepatitis. This child's illness also terminated fatally after a prolonged period. It thus may be that in certain virus infections immunologic factors are of prime importance and that without their action recovery does not take place.

Laboratory Diagnosis of Agammaglobulinemia

From the foregoing it can be inferred that the clinical features of agammaglobulinemia will permit its recognition in most instances. However, laboratory studies are necessary to establish the diagnosis. Specific, of course, are the electrophoretic patterns of the serum proteins obtained by either paper or free electrophoresis. Figure 1 illustrates the typical free electrophoretic pattern of a normal child (a) and one from a child with agammaglobulinemia (a_1). In figure 2 the characteristic paper electrophoretic patterns of a normal person (b) and a person with agammaglobulinemia (b_1) are shown.

Also diagnostic in our hands has been the specific immunochemical determination of gamma globulin using a highly potent specific antiserum prepared by immunizing rabbits against purified electrophoretically homogeneous human gamma globulin.

Obviously, these tests are not regularly available to the general physician. A strong presumptive diagnosis of agammaglobulinemia can, however, be made with the aid of several laboratory tests which *are* generally available.

1. Since patients with agammaglobulinemia are completely lacking in the gamma globulin and part of the $beta_2$ component which normally make up the bulk of the globulin precipitated by the Howe protein-fractionation method (21 per cent sodium sulfate), the serum globulin concentration is very low and the Howe albumin-globulin ratio consequently is extremely high. This is all the more striking, since it is usual for immunologically normal patients with continuing or recurrent infections, as is true of these patients, to have either a very low or reversed albumin-globulin ratio. Even when the 26 per cent sodium sulfate fractionation technic is used the low globulin concentration and the relatively high albumin-globulin ratio are apparent.

2. Kunkel's[34] turbidimetric method for measuring gamma globulin concentration is now generally available as a liver function test and is extremely simple to perform. Patients with agammaglobulinemia regularly have a zero or insignificant turbidity reading when the gamma globulin is measured in this way. In our hands the zinc turbidity test has proved to be a reliable screening test for the diagnosis of agammaglobulinemia.

3. Patients with agammaglobulinemia lack natural antibodies as well as those induced by immunization or infection. Consequently, determination of iso-agglutinin titer against cells of the heterologous blood group may provide a presumptive diagnosis of this disease. For example, agammaglobulinemic patients of blood group 0 whom we have studied lack completely iso-agglutinins against A and B cells. Patients of blood group A have had either no iso-agglutinins or extremely low titers of antibody against B cells, and a patient of group B was completely lacking in antibody titer against A cells. Thus, an excellent screening test for agammaglobulinemia in patients of blood groups A, B and 0 is the measurement of iso-agglutinin titer against cells of the heterologous blood group. This diagnostic tool would, of course, be useless in patients of blood group AB who normally lack iso-agglutinins against the major blood group substances. None of the agammaglobulinemic patients thus far described have been of blood group AB. This procedure is available to all physicians who have access to blood bank facilities since the test can be easily set up by any technician who is familiar with the procedures involved in crossmatching blood. In evaluating the results of this test it must be realized that infants lack iso-agglutinin and that the test may be unreliable in babies less than six months of age.

4. Another simple screening test for agammaglobulinemia is the performance of the Schick test in patients who have had prior immunization against diphtheria toxoid. Since agammaglobulinemic patients fail to produce antibody in response to antigenic stimulation,

the Schick test results remain positive.

The final diagnosis of agammaglobulinemia should, of course, be made by obtaining an electrophoretic pattern on either the plasma or the serum.

Treatment of Agammaglobulinemia

Although this disease has been recognized as an entity for only four short years, its clinical management appears to be quite satisfactory. There can be little question that the very existence of the clinical syndrome recognized as agammaglobulinemia is the result of the general availability of antibiotic and chemotherapeutic agents. Prior to the advent of antibiotics and sulfonamide drugs the extreme vulnerability of these patients to bacterial infection doubtless led to their early demise and the clinical syndrome of recurrent pneumonia, recurrent meningitis, and recurrent septicemia was not expressed. When effective antibacterial therapy became available, recovery of these patients from severe bacterial infections became possible and the deficient resistance could be expressed in terms of many recurrences of bacterial infection. Thus it is apparent that the treatment of acute bacterial infection in patients with agammaglobulinemia invoking the same principles as are efficacious in treating acute bacterial infection in immunologically normal persons is regularly successful. Its basis, of course, is accurate bacteriologic diagnosis and intensive specific treatment. Following these principles it is clear that agammaglobulinemic patients may recover completely from severe bacterial pneumonia, meningitis, septicemia, etc., in spite of their inability to produce antibody.

Prevention of recurrences of bacterial infection in patients with agammaglobulinemia is also possible. Parenterally administered gamma globulin has in these patients a half-life between 25 and 30 days.[35,36] Most of the recurrent bacterial infections can be prevented if a level of gamma globulin between 100 and 200 mg. per cent is maintained. This serum concentration can be achieved by the intramuscular injection of gamma globulin in a dosage of 0.05 gm. of gamma globulin or of 0.3 cc. per pound of the commercial or Red Cross preparation every four to five weeks.*

Replacement gamma globulin therapy, although doubtless the best prophylactic treatment for patients with agammaglobulinemia presently available, has obvious disadvantages. It necessitates injection of a large volume of gamma globulin solution at relatively frequent intervals, which is a painful and unpleasant experience, particularly in the prophylactic treatment of children. In addition, there are theoretical disadvantages, namely, that the gamma globulin provides only passive protection from agents against which the original donors of the gamma globulin possessed high antibody titer. It does not render the agammaglobulinemic patient reactive to organisms which may produce infection.[37] To us it seems surprising that gamma globulin provides as much protection as seems to be the case. Further, the long-term effects of repeated parenteral injections of gamma globulin have not yet been assayed. Thus far no harmful effects have been reported even though in some patients this form of treatment has been used over a three year period.

The destructive pulmonary complications, such as bronchiectasis, which may be present in patients with agammaglobulinemia before the clinical diagnosis is made, appear to limit the effectiveness of gamma globulin in preventing recurrent infections. In one of our patients with agammaglobulinemia and bronchiectasis the use of a prophylactic antibiotic-gamma globulin combination has been quite effective in preventing recurrent infections for more than one year. In a case reported by Zinneman and associates[38] of a patient who did not respond to gamma globulin administration, marked improvement followed prolonged antibiotic prophylaxis, and these workers concluded that in certain adult patients with acquired agammaglobulinemia, prophylactic antibiotic therapy offers advantages over prophylactic gamma globulin treatment.

Several of our patients with agammaglobulinemia have been maintained on prophylactic antibiotics for more than one year without

*In some agammaglobulinemic patients almost double this amount of gamma globulin seems to be required to keep them free of recurrent bacterial infection.

the aid of gamma globulin injections. This prophylactic approach based on alternate use of penicillin and the tetracyclines has thus far proved to be quite satisfactory. However, the hazard of this method of management is that the agammaglobulinemic patient on prophylactic antibiotic therapy might be subjected to more frequent exposure to organisms resistant to the antibiotics being used in the prophylactic regimen. Thus far, infection with resistant organisms has occurred with equal frequency in the patients being maintained on prophylactic gamma globulin and those being maintained on prophylactic antibiotics, and the relative merits of the two methods await future analysis.

It is obvious to us that none of the presently available methods of treatment are entirely satisfactory for long-term management of patients with agammaglobulinemia. Ideal would be the discovery of a method which would overcome the metabolic block in these patients and permit their active resistance to the invasion of microorganisms. Thus far, although recent studies[39] may represent progress in this direction, achievement remains in the future.

Summary

We have described the clinical problem posed by agammaglobulinemia and differentiated between the acquired and the congenital-hereditary forms of the condition. Diseases other than isolated agammaglobulinemia featured by low concentrations of gamma globulin are noted. Clinical manifestations which suggest the diagnosis are presented, as well as the presumptive and definitive laboratory diagnosis. The treatment presently available is pointed out.

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Recent Significant Developments in Intracardiac Surgery

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It is difficult to determine the most significant recent advances in heart surgery. I have tried to select those that are true, sound and reliable and yet are new.

When we think of heart surgery we think first of the heart-lung machine, the extracorporeal system which will permit one to open the heart under direct vision and repair the interior. Such machines exist today and are sufficiently perfected to be used on living human patients. I have just come from Minneapolis where Dr. Lillehei performed a wonderful operation, repairing an interventricular septal defect in a youngster. The child was able to sit up within a couple of hours and to call for its mother. Open heart surgery with an extracorporeal apparatus already is a reality, and you will hear more and more about it.

At least three other such apparatus are ready for clinical use in this country. All of us inevitably will have our vision extended as the medical frontiers are pushed back.

The apparatus which is used in Minneapolis, the De Wald oxygenator, is illustrated in figure 1. It is essentially simple, consisting of a bubbling or oxygenating chamber, a debubbling chamber, a reservoir, and a pump which propels the blood into the body in an oxygenated condition. We can let our imaginations dwell on the future possibilities. All the barriers to major intracardiac repair that have existed previously probably will be dissipated.

Mitral Stenosis

Most of you have heard of me in connection with mitral stenosis, and you may have thought that surgery for mitral stenosis is more or less established and at a standstill and

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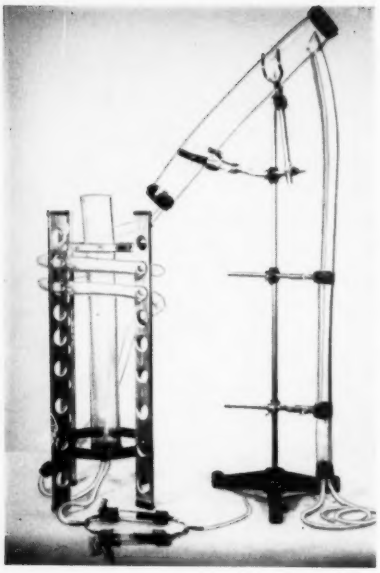


FIGURE 1. De Wald oxygenator in use at the University of Minnesota, Minneapolis, as part of an extracorporeal circulatory system.

that no further advances will take place. That is not quite true. Consider the photograph in figure 2 of an actual specimen of the mitral valve from the ventricular aspect, showing the diminutive orifice. Obviously this lesion is essentially a fibrous stricture which offers great obstacles to current surgical technics.

The classic, accepted treatment for this condition is mitral commissurotomy, ordinarily performed by insertion of the operator's right index finger through an incision made in the left auricular appendage, either to split the fused leaflets apart with blunt digital pressure or to cut them apart with a knife inserted with the finger and guided by it (figure 3).

FIGURE 2. Extreme mitral stenosis. Both papillary muscles may be fused to the valve apex and then must be split extensively if the obstruction is to be alleviated.

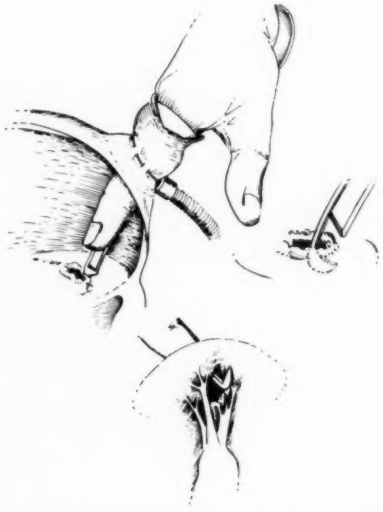


FIGURE 3. Ungloved right index finger of operator inserted through incision in tip of left auricular appendage to split the fused leaflets or guide guillotine knife to divide commissures.

FIGURE 4. Roentgenograms taken before, six months after and seven years after surgery in first case (C. W.) of survival from a modern surgical procedure for mitral stenosis. Note progressive reduction in heart size.

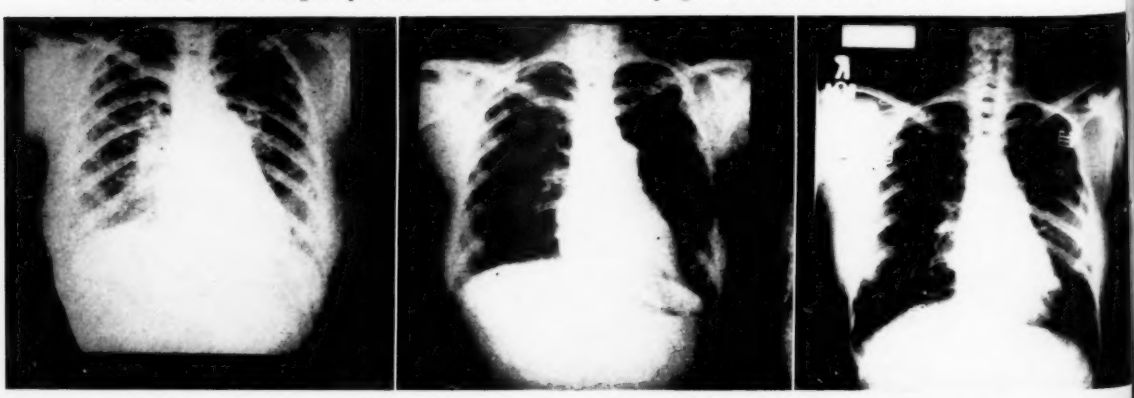


TABLE 1

RELATIVE RISKS INVOLVED IN OPERATION FOR DIFFERENT STAGES OF MITRAL STENOSIS BY LEFT-SIDED APPROACH (RELATION OF CARDIAC RHYTHM TO OPERATIVE MORTALITY, 1,009 CASES OF MITRAL COMMISSUROTOMY)

A.H. CLASS	TOTAL CASES	AURICULAR FIBRILLATION		NORMAL SINUS RHYTHM		TOTAL OPERATIVE MORTALITY (Per Cent)
		Cases	*Operative Mortality (Per Cent)*	*Cases*	*Operative Mortality (Per Cent)*	
I	20	5	0	15	6.5	5
II	359	136	4.4	223	1.8	2.8
III	568	297	13.6	271	5.6	9.9
IV	62	42	16.7	20	15	16.1
TOTAL	1,009	480	11.2	529	4.4	7.6

Roentgenograms of the first patient who survived such an operation are shown in figure 4. It was performed seven and a half years ago. The size of her heart has diminished progressively, and at present I think all of us would consider it entirely normal. We do not know how long she will be all right, but seven and a half years have elapsed and we may hope it will be 70 years.

For the first 1,009 patients (we have operated on more than 1500 in our clinic) operated from the left side, the over-all mortality was 7.6 per cent, being significantly higher among those with auricular fibrillation and lower for those with sinus rhythm (table 1).

Most cardiac surgeons frequently have been disappointed in their technical accomplishment in opening the mitral valve. I was able to open both valve commissures (both extremities of the valves slit) in only 33.1 per cent of the first 811 patients I operated on; the enlargement in the others was limited to one extremity (table 2). So we were not satisfied. We feared that the stenosis might recur in some of these cases, and we considered different technical approaches to the valve because failure to open the valve satisfactorily appeared to be only a matter of technic. Surprisingly, we found, because of the necessity of removing the right lung of a patient with bronchogenic carcinoma at the time of doing a commissurotomy, that one can operate on the mitral valve from the right side.

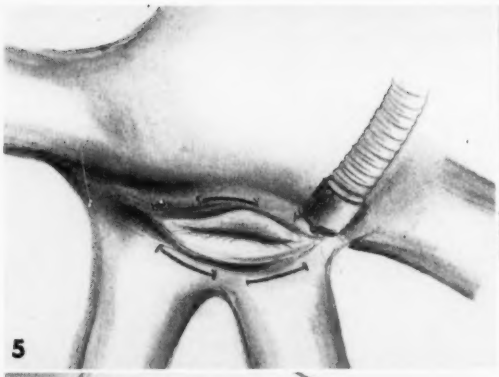
Figures 5 through 7 show how it is done. Just anterior and medial to the junction of the right pulmonary veins, there is a groove which represents the line at which the two external atrial walls turn in to form the septum. This sulcus can be dissected to form a tunnel and can be protected by a purse-string suture and a tourniquet. One can separate the two layers of the septum for a distance of 2 or 3 cm. The index finger can then be inserted into the apex of this dissection and a broad-bladed knife slid along the finger to cut directly into the inner wall of the left atrium (figure 6). Of course, the purse-string suture restrains bleeding, but in addition the finger tip immediately tamponades the opening into the chamber and then wriggles its way through so that it can reach the region of the mitral valve.

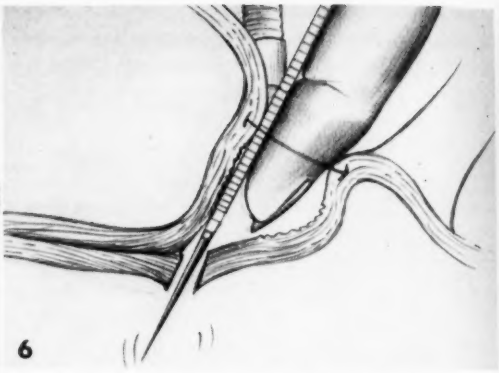
TABLE 2

RELATIVE TECHNICAL ACCOMPLISHMENT IN OPERATIONS FOR MITRAL STENOSIS PERFORMED RESPECTIVELY BY THE LEFT-SIDED AND THE RIGHT-SIDED ROUTES

	LEFT-SIDED APPROACH *(1200 Cases)*	RIGHT-SIDED APPROACH *(196 Cases*)*
Both commissures opened	33.1%	97.3%
One commissure only		
Anterior	65.0%	1.6%
Posterior	1.9%	1.1%
	100.0%	100.0%

*Four cases, operative data not complete.





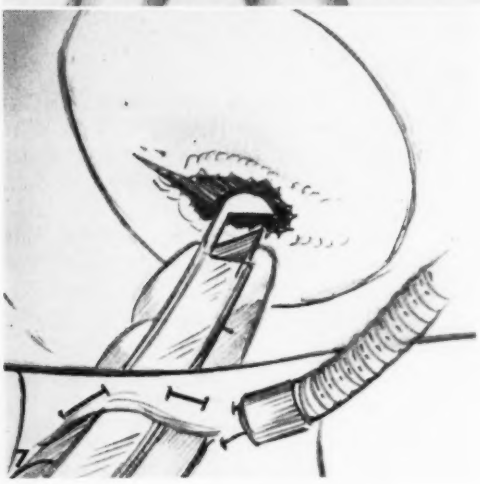


FIGURE 5. Limited dissection of interatrial septum. A purse-string suture is placed deeply in the tissues for hemostasis.

FIGURE 6. Broad-bladed scalpel is guided along palmar surface of bare left index finger which has been inserted into apex of dissected interatrial septum to pierce the lower (left) half of the septum and to enter the left atrial chamber.

FIGURE 7. If commissures cannot be split digitally, long guillotine knives are inserted into heart along finger to divide commissures. Note that the so-called "posteromedial" commissure really should be designated as the right lateral commissure and is correspondingly much easier to attack with the right-sided approach.

Approaching the mitral valve in this fashion, the slit will be found to run essentially horizontally. The posteromedial commissure, which is so difficult to split using the usual left-sided approach, is amazingly easy to separate (figure 7). Furthermore, incompetence and regurgitation rarely are produced when this commissure is attacked through a right-sided incision. Because of the technical difficulties associated with the left-sided approach, a high percentage of these patients develop regurgitation when the posteromedial commissure is opened with an instrument. There is no difficulty in opening the anterolateral extremity of the valve by the right-sided route. Among the first 196 patients operated on by the right-sided procedure, we failed to open both commissures widely in only five. We therefore have achieved a valve opening which ranges from 33 to 200 per cent larger than the usual one obtained from the left.

With this more adequate enlargement of the valve orifices we will expect a lower incidence of recurrence of stenosis and a much higher rate of clinical improvement. Our early experience (over one year's duration) thoroughly corroborates this hope.

Tricuspid and Aortic Stenosis

Rheumatic disease, of course, is not limited to the mitral valve; it affects the myocardium and it also affects two other valves, the tricuspid and the aortic. Figure 8 is a photograph of a stenotic tricuspid valve showing how the three leaflets have become fused together at their natural commissures just as is the case in mitral stenosis. This aperture should admit two or three fingers; in this case it will barely

FIGURE 8. Typical rheumatic tricommissural fusion of the tricuspid valve.

FIGURE 9. Typical rheumatic tricommissural fusion of the aortic valve.

FIGURE 10. Transventricular splitting of fused aortic commissures by the use of a special triradial dilator.

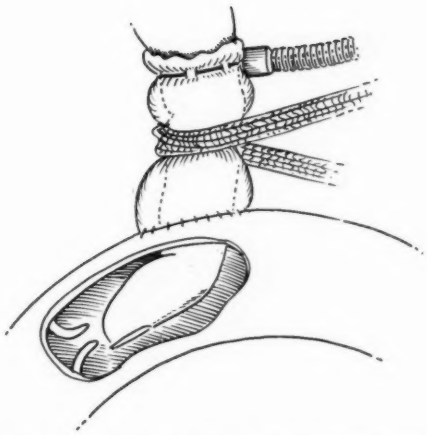


FIGURE 11. Transaortic approach to aortic valve using a pouch of pericardium which has been sutured to an incision made in an excluded portion of the ascending aorta. This permits either digital separation of the commissures or the guidance of an instrument to divide or split the commissures.

admit a lead pencil. When we operate on the mitral valve from the right side, the natural approach to the tricuspid, the right auricular appendage, is readily found in the operative field. It projects forward, and it is a simple matter to insert the left index finger through an incision made in its tip to feel the tricuspid valve. To our amazement (and yet this is a reflection on our former lack of knowledge of pathology), we found that 10 per cent of patients with apparently isolated mitral stenosis have coexisting severe tricuspid stenosis. This usually has not been diagnosed preoperatively, so now we routinely explore every tricuspid valve when we operate on the mitral valve from the right side. In 10 per cent of these patients we then operate for tricuspid stenosis. You can readily see that the left-sided approach, which for practical purposes does not permit tricuspid exploration, immediately eliminates 10 per cent of patients from the possibility of obtaining really good clinical results.

The aortic valve also is subject to rheumatic deformation. Figure 9 illustrates a classic example of tricommissural fusion of an aortic valve. You can see the remnants of the commissures. This valve is somewhat calcified, as are most such stenotic aortic valves. There is progressive reduction in the size of the outflow passageway of the left ventricle until only a trickle of blood can be ejected with each heartbeat. The patient, usually a man in his forties or thereabouts, is incapacitated, anginal pain develops, and death occurs suddenly because of relative coronary insufficiency.

At one time we recommended a transventricular approach to this valve, using a tribladed dilator which, once passed through the diminutive opening, could be spread apart to separate the commissures (figure 10). Today we feel that this method is unduly dangerous because some of these valves are not tricommissural but are bicommissural. A triradial dilator then may produce incompetence and perhaps death. Further, the left ventricle is irritable and ventricular fibrillation is likely to develop during the surgical manipulations.

Today we approach the valve by way of the ascending aorta (figure 11). We exclude a portion of the aortic wall; we incise the excluded portion for a distance suitable for the admission of a finger and an instrument, and then suture a pouch of pericardium to the opening created in the aortic wall. The ungloved finger (and we do all our intracardiac work now with ungloved fingers, because one can feel several hundred per cent better without a glove than with one) is inserted into this pouch which has been sutured to the aorta, a peripherally placed purse-string suture being tightened to provide hemostasis. The clamp is removed from the aorta, and the finger is passed into the lumen and down to the region of the valve. One can readily find the valve opening because blood spurts out of it with each heartbeat.

In perhaps 40 to 50 per cent of these cases the surgeon will be able to split one or more of these commissures apart by digital pressure alone, making instrumentation unnecessary. In the remainder, an instrument of some type —either a cutting instrument or a dilating instrument—is guided into the aorta alongside the finger to enter the diminutive valve opening to cut or split apart one, two or three of the fused commissures.

To date we have operated on 331 patients for aortic stenosis. Of these operations, 225 were done by the transventricular approach with a mortality, we are sorry to admit, of 27.5 per cent (table 3). We do not believe that this method ever can give us satisfactory mortality statistics, and we are not too happy with some of the clinical results in this group.

There were 16 deaths among 106 patients operated on by the transaortic approach, a mortality of 15.1 per cent (table 3). This rate is only half that of the older technic, but we think we can do a lot better because there were many early technical difficulties with the pouch. There was serious bleeding in a number of instances. I am quite sure the risk can be reduced to less than 10 per cent, and I believe our next hundred cases will justify that faith.

Operations on all three of these valves (mitral, aortic, tricuspid) can be performed through a right anterior thoracic incision (figure 12a). By comparing the photographs in figures 12b and 12c, one sees that the right-

TABLE 3

OPERATIVE MORTALITY ASSOCIATED WITH TRANSVENTRICULAR AORTIC COMMISSUROTOMY AND WITH AORTIC COMMISSUROTOMY PERFORMED BY THE SUPRAVALVULAR ROUTE

	TOTAL CASES	DEATHS	
		Number	*Per Cent*
TRANSVENTRICULAR AORTIC COMMISSUROTOMY			
Original aortic dilator	11	2	18
Bailey aortic dilator			
Isolated aortic stenosis	78	23	29
Aortic stenosis with mitral disease	106	22	21
Aortic stenosis, aortic insufficiency	7	4	57
Aortic stenosis, aortic insufficiency with mitral disease	23	11	48
	225	62	27.5
TRANSARTERIAL AORTIC COMMISSUROTOMY			
Isolated aortic stenosis	72	10	14
Aortic stenosis with mitral disease	28	5	18
Aortic stenosis, aortic insufficiency	5	1	20
Aortic stenosis, aortic insufficiency with mitral disease	1		
	106	16	15.1

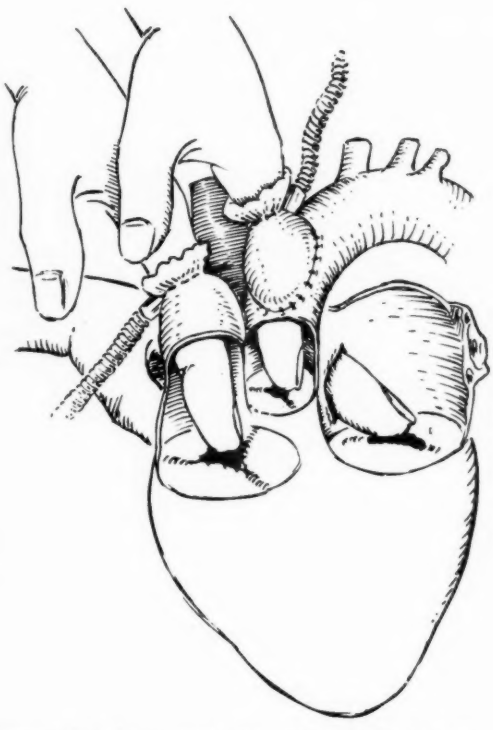


FIGURE 12a. Diagrammatic illustration of right-sided approach to all three valves (mitral, aortic, tricuspid) which are subject to rheumatic deformation.

FIGURE 12b. Usual long left posterolateral incisional scar from left-sided approach to the mitral valve.

FIGURE 12c. Anterolateral incisional scar resulting from operations on one, two or three valves when approached from the right.

FIGURE 13. Photograph of incompetent mitral valve (autopsy specimen). Note that shrinkage or retraction of the posterior portion of the leaflets or dilatation of the mitral ring (annulus fibrosus) causes incompetence of the posterior pole of the valve.

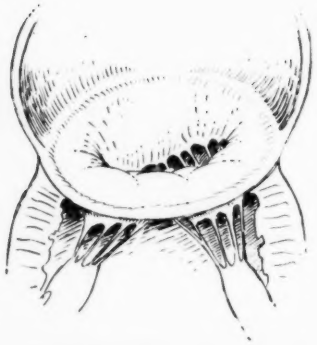


FIGURE 14. Diagrammatic illustration of same condition as in figure 13.

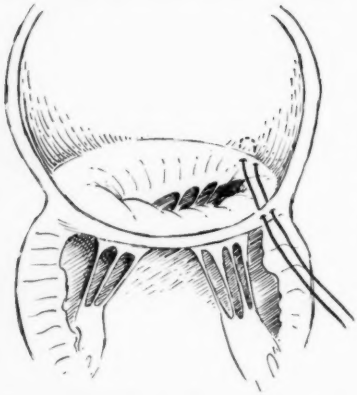


FIGURE 15a. Nichols' method of placing a cross-plicating mattress suture across the incompetent pole of the mitral valve.

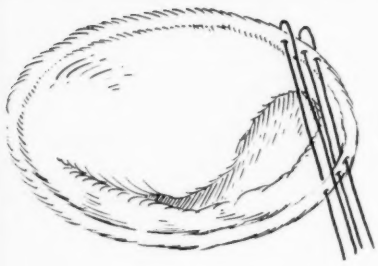


FIGURE 15b. Second such suture placed.

sided approach is quite satisfactory esthetically. The important thing, however, is not the appearance but the fact that one does not cut across the latissimus dorsi and the other back muscles, as entailed in the longer posterolateral incision which must be used when operating from the left side.

Mitral Regurgitation

Figure 13 demonstrates something which to me is even more dramatic than anything I have said, because it is the solution to a problem I was unable to solve. It shows a mitral valve removed at autopsy. There is severe regurgitation. The front half of the valve is competent and the leaflets can be approximated in that region. The posterior half, how-

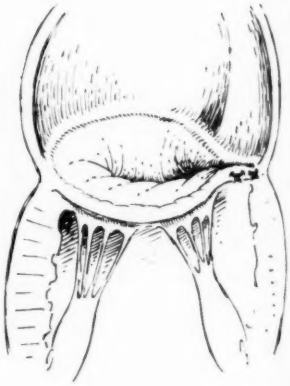


FIGURE 16. On tying down these sutures, the opposed portions of the annulus fibrosus are brought into firm contact. Hence, since the attached basal portions of the valve cusps then come into contact, the free margins are brought into a position from which they can coapt during systole.

ever, is incompetent because of shrinkage of the leaflets so that they cannot close fully during ventricular systole. As some of you know, I have worked very hard on this problem over the past six years. I have tried many operative approaches, all of them equivocal in their ultimate accomplishments. We certainly have not been happy with them. One of my associates, Dr. Henry Nichols, apparently has the solution to the difficulty.

The diagram in figure 14 represents the same situation as seen in figure 13; the valve is incompetent posteriorly, the leaflets retracted. Figures 15a and 15b demonstrate what Dr. Nichols does. He passes a mattress suture across the posterior (incompetent) pole of the valve, piercing the annulus fibrosus. Then he places a second suture a little bit posterior to the first. These are tied down, and note what happens (figure 16)! This portion of the valve, since its basal attachments are brought closer together, becomes competent. The free margins of the valve simultaneously have been brought closer together and rendered capable of systolic coaptation. The finger in the heart can appreciate immediately that the regurgitant jet has been abolished. Nothing like this dramatic abolition of the regurgitant jet had been observed in any previous procedure. This new technic has been applied in over a dozen cases and has abolished the regurgitation in half of them and reduced it enormously in the other half. I am quite convinced that this is the surgical answer to this problem. I believe it will prove just as satisfactory for this previously intractable condition of mitral regurgitation as commissurotomy is for mitral stenosis.

Aneurysm of the Aorta

The diagram in figure 17 illustrates how a segment of the thoracic aorta may be replaced with a homograft from another person. Figure 18a shows such an aneurysmal specimen after removal. Measurement of the specimen indicated the enormity of the lesion. Preoperative and postoperative x-rays are shown in figure 18b. There is some residual pleural reaction, but the aneurysm is gone. More than two years postoperatively, this woman has completely normal health as far as anyone can tell. This represents a tremendous advance in treatment of these lesions, and Dr. DeBakey of Houston and Dr. Lam of Detroit and others who have pioneered this work deserve immeasurable credit. I should also mention Dr. Gross of Boston who used grafts of the aorta in the treatment of coarctation long before anyone applied this technic for an aneurysm.

A different kind of aortic aneurysm which all of you have encountered is the dissecting aneurysm (figure 19). In this condition, due to a fracture of the intima and disease of the media, blood extrudes out of the lumen and separates the wall of the aorta, splitting it down toward the iliacs, usually, until it finally ruptures through the adventitia, causing fatal hemorrhage. Occasionally it ruptures back through the intima, producing a double-barreled aorta and a clinical cure. For a long time we thought we would treat a dissecting aneurysm in the same manner as any other, by resection and replacement with a homograft.

Figure 20 is an aortogram showing a double lumen of the aorta, a finding which is pathognomonic of dissecting aneurysm. This man had the usual severe pain and shock associated with onset of this disease. I thought I would place a homograft and take out the aneurysm. On opening the thorax, this is what I saw (figure 21)—this great, angry, red, sausagelike thing with hemorrhagic areas extended down to and through the diaphragm into the abdomen. Obviously there was no way to place a graft; all the thoracic aorta was dissected. Dr. DeBakey of Houston had already solved this problem and reported it at a medical meeting I had attended. Therefore I knew just what to do and forthwith did it. I cross-clamped the dissected aorta above and below, and opened the outer lumen and milked out the jellylike, partially clotted blood until we had a double tube showing (figure 22a). I then divided the inner tube which contained the intima and a portion of the media and sewed the lower segment of it all around to the outer wall of the lower aorta. The outer wall was then repaired. I left the upper portion of the inner tube open, as shown in figure

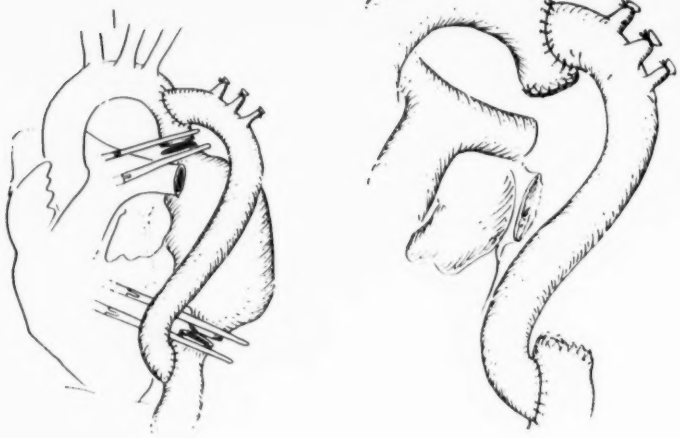


FIGURE 17. Diagrammatic method showing resection of a large aneurysm of the thoracic aorta by the use of an aortic homograft anastomosed above and below in oblique end-to-end fashion. This obviates the need for a shunt or the use of hypothermia.

22b. Now you can see that blood will come out of the aortic lumen, will get into this dissected space, but when it reaches the line of anastomosis it necessarily must be directed back into the normal lumen (figure 22c). That is the way nature cures an occasional case by permitting the blood to break back into the natural lumen. This patient made a good recovery; he is back home and apparently is without symptoms. He still has a markedly enlarged thoracic aorta, but we do not intend to do anything about it.

Myocardial Infarction

The last condition I want to talk about is something which is fresh in all our minds. It

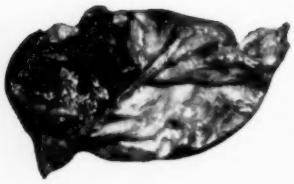
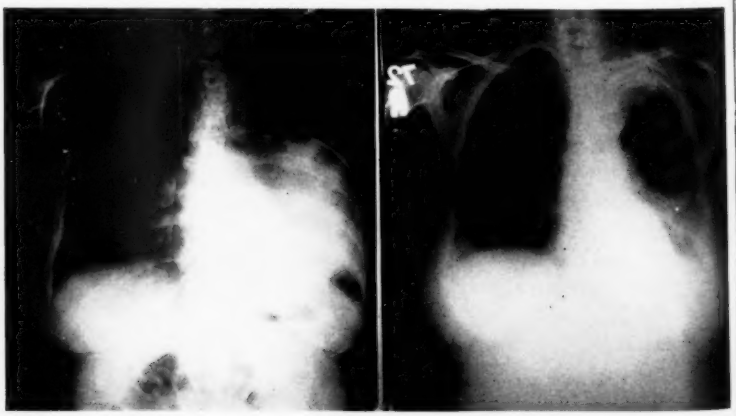


FIGURE 18a. Aneurysmal specimen after removal.

FIGURE 18b. Preoperative and postoperative roentgenograms of the thorax.



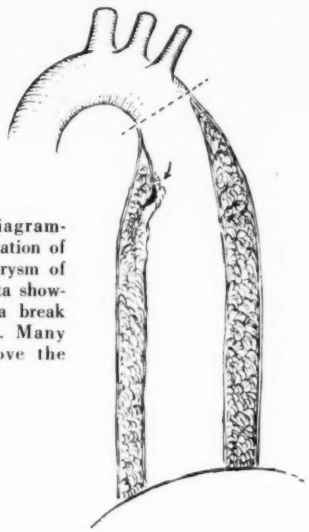


FIGURE 19. Diagrammatic representation of dissecting aneurysm of descending aorta showing origin at a break in the intima. Many start just above the aortic valve.

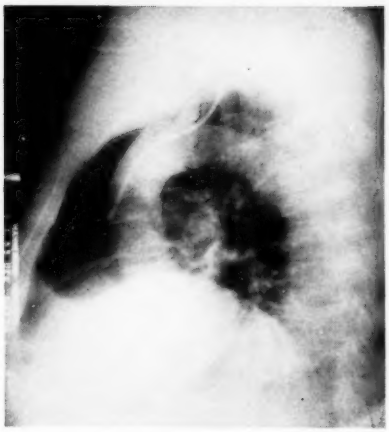


FIGURE 20. Aortogram showing double lumen pathognomonic of dissecting aneurysm.

FIGURE 21. Photograph showing large dissecting aneurysm of entire descending thoracic aorta as exposed at thoracotomy.

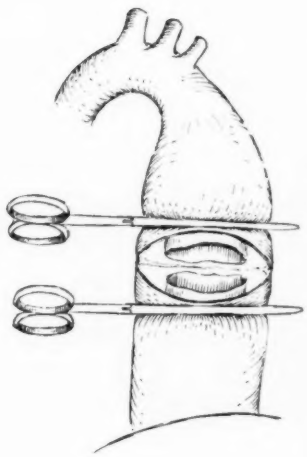


FIGURE 22a. After cross-clamping above and below, the vessel is opened and the inner tube is divided.

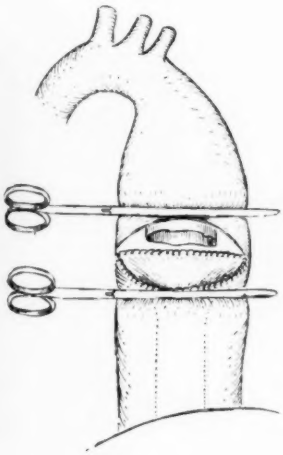


FIGURE 22b. The cut end of the lower segment of the inner tube is sutured to the outer tube in complete circumferential fashion.

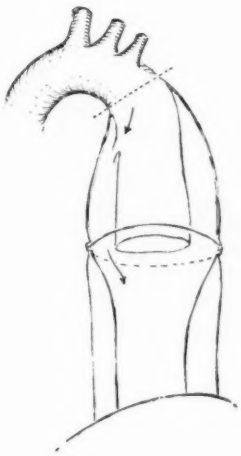


FIGURE 22c. Correction of dissection of aorta by rerouting stream into inner lumen.

FIGURE 23. Partial-thickness infarct of left ventricular wall.

illumination of light. But it is tough and strong and maintains functional continuity of the myocardium over the region where the muscle has been destroyed. The remaining myocardium then can function, and since there is a great reserve in all our muscles, the heart usually can compensate so that satisfactory recovery can be obtained. We all trust that will be the case with our President.

In a certain unfortunate group, variously estimated as from 5 to 20 per cent of all myocardial infarctions, there is such thinning of the ventricular wall that aneurysm formation occurs. A left ventricular aneurysm is a terri-

FIGURE 24. Healing of infarct with thin but strong scar of ventricular wall.

is the President's disease. Figure 23 is a photograph taken from one of the standard textbooks of pathology showing a partial-thickness infarct of the left ventricular wall. As you know, these can be full-thickness infarcts, but some of them are partial-thickness infarcts, as we hope and trust the President's was.

With the passing of time and natural healing processes, a scar is formed, as shown in the autopsy specimen in figure 24. There is replacement of the dead tissue by fibrous connective tissue. It may not be too thick; it may be thin enough, as in this case, to permit trans-

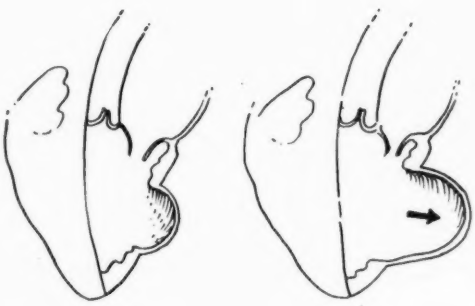


FIGURE 25. Diagrammatic representation of physiologic effect of ventricular aneurysm showing that the sac must be distended with blood before any can be expelled into the aorta.

ble thing, because the contraction of the ventricle must balloon out the sac before it can expel any blood into the aorta (figure 25). Pulsatile movement of the aneurysmal wall develops with dilatation during systole. During diastole it collapses and its contained blood partially fills the left ventricle, hampering the entrance of blood from the mitral valve. The result is a massive mechanical handicap to forward propulsion of the circulation. These persons, in contrast to the average patient with an infarct who has 12 years to look forward to, have less than three. They will suffer most of that time with severe angina, severe shortness of breath, ever-impending congestive heart-failure, and perhaps thrombo-embolic phenomena, since clots often form in these sacs and may become dislodged.

In April 1954 a 54 year old coffee planter from São Paulo, Brazil, came to us with a history of a myocardial infarction a year previously. On the oblique roentgenogram (figure 26) you can see that he had a large aneurysm of the left ventricle. He had had hardly a day free of pain since his infarction in February 1953. When he came to us he would have been unable to walk from one side of this platform to the other because of dyspnea. He

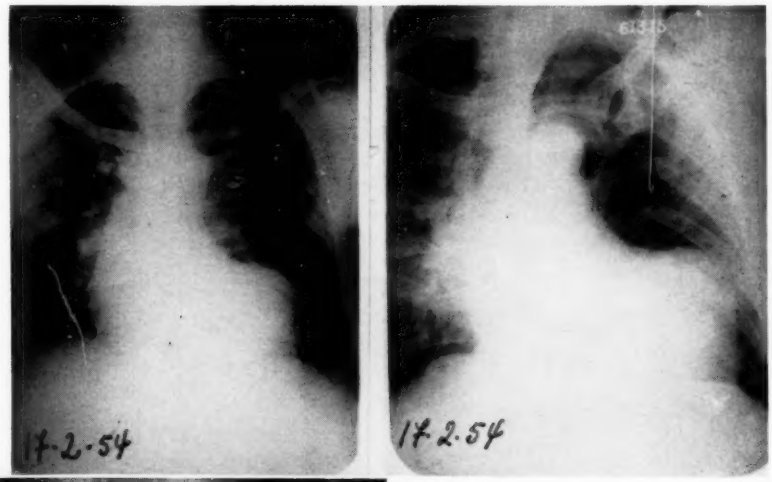


FIGURE 26. Postero-anterior and oblique roentgenograms of patient with large left ventricular aneurysm.

FIGURE 27. Anterolateral left ventricular aneurysm exposed at thoracotomy (and pericardiotomy).

FIGURE 28. Diagrammatic representation of technic employed in resecting this aneurysm.

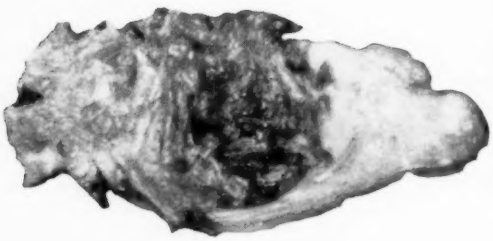


FIGURE 29. Resected specimen.

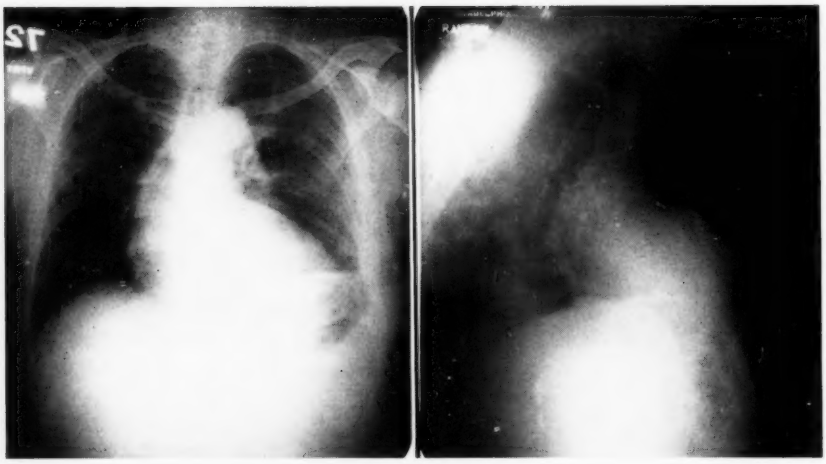


FIGURE 30. Postoperative roentgenograms indicating removal of aneurysm.

had four pillow orthopnea. Recently a diastolic gallop rhythm had developed—that frequent precursor to death. He took nitroglycerin tablets 20 or more times a day for relief of angina.

After preparing him for six weeks (he still had gallop rhythm and shortness of breath but perhaps less hepatic enlargement) we did a left thoracotomy. The aneurysm we found is seen in figure 27; there was no neck; it was just a large bulging sac apparently taking up the entire anterolateral aspect of the left ventricle of his heart.

Essentially the procedure we performed is shown in figure 28. We placed clamps across the base of the bulge. Three layers of mattress sutures were placed in the myocardial wall, two of them before we excised the aneurysm and one afterward. Probably three layers were excessive, but at the time it seemed to us that three were none too many.

The interesting thing about this case was that at the very moment the base of the sac was clamped, the blood pressure, which had been hovering around 80 mm. Hg systolic, rose to 120. The pulse rate, which had been about 120 per minute, dropped to 80. The physiologic removal of that sac from the circulation alone was enough to accomplish a great improvement in the patient's cardiodynamic balance.

The resected specimen is shown in figure 29. It is almost 4.5 in. long and 3.5 in. wide. There is some clot in its center.

Radiographs taken six weeks later, just before the patient's discharge from the hospital, show the absence of aneurysmal bulging (figure 30). This man has returned to his home and is now almost 20 months postoperative. He no longer takes nitroglycerin. The gallop rhythm disappeared within five days following surgery, and he has had no more signs of heart-failure.

Inasmuch as we did not perform revascularization surgery in this case, I think the removal of this aneurysmal sac alone accomplished the good results that were achieved. Since then, similar procedures have been carried out twice in other cases. We believe that all these unfortunate individuals should be treated in like fashion, preferably before they enter the last stages of their disease.

41st INTERSTATE POSTGRADUATE MEDICAL ASSEMBLY

Cleveland, Ohio, October 22-25, 1956

The Diagnosis and Management of Placental Insufficiency

Presenting the problem of neonatal postmaturity as it differs from the problem of obstetrics *post datism*. In the former situation the fetus has outgrown the aging placenta and begins to suffer from a relative placental insufficiency. The entity occurs in about 2 to 3 per cent of all deliveries and is associated with a fetal loss ranging from 10 to 15 per cent.

ALLEN CAMPBELL BARNES, M.D.

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The Present Status of Surgery in the Treatment of Cancer

GEORGE CRILE, JR.

Cleveland Clinic, Cleveland

GEORGE CRILE, JR.

FIRST I should like to clarify my position on some general aspects of diagnosis and treatment of cancer and to emphasize that I do not advocate, nor have I ever advocated, a system of public education about cancer which teaches patients a philosophy of fatalism in regard to their disease or to their symptoms. I am a surgeon and I have confidence in surgery in the treatment of selected patients with cancer. Moreover, I believe that when the patient comes to the physician early, the problem of treatment is more easily solved.

I also believe that many lives are lost because patients are taught and overtaught that their lives depend to a large degree on prophylactic surgery and on radical surgery before the necessity for such radical surgery is clear. I am not referring to cancerphobia in terms of psychiatric states; I am speaking of the physical harm that comes from overtreatment. All of us, not only in surgery but also in medicine, know from bitter experience that overtreatment can be just as dangerous as undertreatment. In short, it is a middle-of-the-road policy that I am advocating.

If teaching fear of cancer, and urging that the widest possible operation be done at the earliest possible moment were the answer to the problems of cancer, one would expect to see a favorable trend reflected in vital statistics on cancer. But, as you know, no improvement in vital statistics has taken place except in a few isolated instances, notably in cancer of the cervix, which, perhaps because of better hygiene, perhaps because of prophylactic treatment of cervicitis, or perhaps because of the Papanicolaou stain and early detection of cancer *in situ*, is showing a genuine fall. Aside from that, however, the trends are very mixed, rising, as you know, in cancer of the respiratory tract, falling, for some totally unexplained reason, in cancer of the stomach—a

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decrease that certainly is not related to the success of treatment, because treatment is hardly any more successful in this particular disease than it ever was. It is the actual incidence of stomach cancer which is falling.

But can our failure to decrease the death rate from cancer be correlated with the reported rising cure rate of cancer? I think that McKinnon[1] in Canada, who has done so much work along these lines, has answered this question by stating that curing cancers that would not have been fatal, even if untreated, does not alter the death rate from cancer. Take cancer of the skin as an example. Long ago, when only the large and serious cancers of the skin were treated, small basal cell cancers were left alone. Yet, the death rate from skin cancer in those days probably was not much higher than it is today. Today we are curing many more cancers of the skin because we are removing many more basal cell cancers, but many of these would not be fatal even if they were left untreated. Certainly cancer of the skin is more easily treated when it is operated on early, at a time when it can be removed with a relatively small operation, and in some cases perhaps before metastases have taken place. But throughout the entire field of cancer there is strong evidence that there is a factor of biologic predeterminism; in other words, from the time certain cancers are clinically recognizable, they are, like basal cell cancers, preordained to remain localized, while others, like melanomas, may spread into the circulation even before the primary tumor is noticeable.

There is much evidence to support the theory of predeterminism. Some of it comes from the experimental laboratory, some from the clinic. One of the most striking supports is the observation of Engel,[3] in Sweden, who studied the blood in the veins that drain operable cancers of the stomach, colon, lung and breast. At the time of operation 58 per cent of the patients with these cancers had cancer cells in the blood draining the affected part. These cells were clearly demonstrable by cytologic technics. Engel found that if you break this figure down according to the grade of malignancy, cancer cells are demonstrable in the blood in some 35 per cent of the grade 2 cancers, in 78 per cent of the grade 3, and in 100 per cent of grade 4. Since these were operable cancers, Engel's observation suggests that many cancers are systemic diseases, probably from the very first and long before the cancer is clinically recognizable.

Remember how long it takes for a cancer to become clinically apparent. Think of the very high degree of malignancy of a melanoma which may be no bigger than a pinhead and which has been present as a clinical tumor perhaps only a few days or weeks. The patient may have just noticed this growth, yet how high is the mortality rate from this type of tumor. And then think of the average size of a cancer of the stomach at the time that it is first detectable by clinical symptoms or by x-ray; it is a large tumor, often as big as a saucer. If this cancer of the stomach is of a highly malignant type and has, like a melanoma, a tendency to invade blood vessels, the course of the cancer is preordained long before the surgeon ever sees the patient. On the other hand, if the cancer of the stomach is such that, like the basal cell cancer, it is preordained to remain localized for a long time, then it probably will remain localized almost indefinitely unless it is disseminated by surgical intervention.

Operation is, of course, necessary in many of these cases. Naturally, an obstructing carcinoma at the pyloric end of the stomach must be removed, because the mechanical obstruction makes removal of the tumor essential for survival. But remember, the operation has two possible effects: One is a great potential for good, the possibility of completely eradicating those cancers that are localized and that have not already disseminated themselves widely throughout the system; the second is the danger that even a localized cancer can be disseminated and implanted by operation and that its course can be greatly accelerated, so that the patient dies very much sooner as the result of the breaking of the natural barriers of host resistance.

The factor of host resistance is important. As long as 40 years ago, Jones and Rous[4] took a transplantable mouse carcinoma, made

a suspension of living cancer cells, and injected it into the abdominal cavities of mice that were susceptible to the cancer. There were no takes in the normal animals; the natural resistance of the peritoneal cavity was sufficient to destroy the foreign cells. But when Jones and Rous put a silicate powder in the peritoneal cavity and a week later injected cancer cells, the animals developed carcinomatosis of the peritoneum. When Jones and Rous put a tiny glass rod in the peritoneal cavity and then injected the carcinoma cells, the cancer implanted itself exactly at the site of the glass rod and nowhere else in the abdominal cavity.

This immediately suggests an explanation for the so-called Krukenberg tumors of the ovary, which occur so commonly in women in the reproductive age and which usually are associated with infiltrating carcinomas of the stomach. It has been shown cytologically that scrapings from the peritoneal surfaces of infiltrating cancers of the stomach and colon show viable cancer cells. Even in localized gastric cancers, if they have extended through the wall of the stomach to involve the serosa, smears of peritoneal fluid or of saline washed over the peritoneal surface of the cancer often show cancer cells. Ascitic fluid in patients with extensive cancer is filled with cancer cells. Perhaps this wide distribution of cancer cells and their tendency to localize and grow at sites of injury explain why Krukenberg's tumor of the ovary occurs only on the ovary; and why the rest of the peritoneum is free of carcinoma. Since this tumor occurs in ovulating women, it is likely that the trauma of ovulation, when the peritoneum is broken, determines the site of the implantation.

If irritation of the peritoneal cavity or the trauma of ovulation can make the peritoneum susceptible to cancer, what does an operation do? When we open the abdomen of a patient who has cancer, does the trauma favor the growth of implants? Naturally, if the patient has cancer cells all through his abdominal cavity, he is not apt to survive indefinitely; sooner or later these cells are very likely to implant and grow. But in some cases surgical intervention, even if it is only an exploratory operation or a biopsy, may make it possible for the cancer to implant itself and to grow much more rapidly than it would in the natural course of the disease. In weighing the pros and cons of operations we must consider what we are doing to lower the natural resistance of the patient to his disease.

This immediately brings up very serious considerations in operations for such cancers as those of the stomach, where the curability rate in the natural course of the disease is quite low. Perhaps various cancers of the stomach are as different from one another as is basal cell cancer of the skin from melanoma. Perhaps there is a group of low-grade cancers of the stomach, like basal cell cancers, that do not metastasize and another small group of middle-grade cancers, like squamous cell cancers of the skin, which have their own peculiar properties of metastasizing only to the lymph nodes and not systemically. Perhaps these types, as well as those of high malignancy, are present in the spectrum of diseases we call "cancer of the stomach," "cancer of the breast," and "cancer" everywhere. We know that this is true in cancers of the skin, and we know it is true in cancers of the thyroid where an equivalent to "basal cell" cancer occurs in the thyroid of one in every 200 people and which almost never causes trouble. There is the equivalent of a "squamous cell type," which we call papillary carcinoma of the thyroid, which metastasizes almost exclusively to the regional lymph nodes. And, finally, there is a highly malignant undifferentiated group of cancers which metastasize everywhere. If this is true of the cancers of the accessible organs about which we know the most, it is probably also true of many other organs.

Perhaps we should not consider cancer of the stomach as an entity any more than we think of cancer of the skin as an entity. We must find some way of determining before operation whether we are dealing with a low-grade, basal cell type of cancer of the stomach or with an intermediate or highly malignant type. Our challenge is to find out how to recognize clinically which type is which. Already we recognize that certain cancers of the breast, like the inflammatory carcinomas, are not

curable by operation. Perhaps the infiltrating "leather bottle" type of cancer of the stomach is the gastric equivalent of inflammatory carcinoma of the breast and should not be operated on except to relieve obstruction. Certainly, in the serous cavities harm is done by resecting and disseminating certain types of cancers that are not adaptable to surgical intervention.

Since the blood vessels of highly malignant cancers are filled with cancer cells, manipulation may liberate more cells. Fisher and Turnbull[5] took six samples of blood from the mesenteric vein of a cancer of the rectum, before the tumor was disturbed, and found no cancer cells present. Then a resident was asked to do a rectal examination and palpate the cancer. While the examination was going on, blood again was taken and was found to be filled with clumps and lumps of cancer cells.

These are vital considerations. In the midcolon it is simple to avoid the possibility of manipulative spread by complete ligation of the entire blood supply before the cancer itself is touched or manipulated. Cole, Packard and Southwick[6] have shown the grave danger of implanting cancer cells from the lumen of the bowel itself. The high incidence of local recurrences following low anterior resection of cancer of the colon is now attributed largely to implantation of cells. Moreover, it appears that the use of the antibiotics, which have done so much to reduce the immediate mortality rate of operations on the colon, is one of the factors that is increasing the implantability rate of colonic cancer. Patients who before might have died of bacterial peritonitis now are dying later of carcinomatous peritonitis. Patients whose anastomoses before the use of antibiotics might have leaked because of infection and improper healing now are developing recurrences of cancer, because the cancer cells survive more readily when the contents of the colon are sterile.

This clinical observation has been checked in the experimental laboratory in Holland by Vink,[7] who took a transplantable rabbit carcinoma, injected a suspension of it into the rabbit's large intestine, and then a few minutes later resected the intestine below it. He found that in those rabbits that had had no antibiotic preparation there were only a fourth as many local recurrences of the cancer at the site of the anastomosis as in those that had received antibiotics.

What I am trying to point out is that operations for cancer have great potentialities for doing harm as well as for doing good. Often, operations are necessary, and if they are properly planned and executed they can cure cancers and save lives; but we must not forget that they can also shorten lives. From time to time, all of us have seen patients who have cancers of the stomach, or of some other organ, which for some reason were considered to be inoperable, yet to our astonishment these patients lived on for many years. I have seen patients with what were considered to be inoperable cancers of the stomach live for more than five years. One such patient finally came to operation because of obstruction, yet the cancer was still localized and operable at the end of five years. Within six months prior to time of operation, the cancer which had remained localized for more than five years spread rapidly; the patient developed carcinomatous peritonitis and died.

We have seen this same thing occur in the thyroid. In more than 60 per cent of all patients who had low-grade papillary carcinoma cut into or biopsied at the time of operation, subsequent operation showed implants of the cancer in skin, subcutaneous tissue or muscle remote from the thyroid itself.

These are some of the reasons why we must be careful in our operations. For a long time we have recognized that in the breast we cannot cut into cancer without implanting it. We know that after the biopsy we have to change our instruments and our gloves before we do a radical mastectomy. This principle is recognized in the breast, but in the abdomen most of us do not hesitate to take biopsy specimens of lesions which still are operable. Surgeons operating on cancers of the colon that are localized and perfectly operable but have metastases in the liver, may reach up and remove biopsy specimens from these metastases, thereby perhaps disseminating cells throughout the peritoneal cavity. The possibility of implant-

ing and disseminating cancer must always be considered. Perhaps it is some of the positive things that we are doing that spread cancer and make us less successful than we would like to be in controlling the mortality rate from this disease.

Cancer of the Breast

The wisdom of routine removal of lymph nodes involved by cancer is open to question. I am going to speak about cancer of the breast now because this is one of the most studied of all cancers. It is located where we can see it and feel it. The diagnosis of cancer of the breast is not difficult to make; at least sooner or later it becomes clear, and the vital statistics on breast cancer are much more accurate than those on intra-abdominal cancer, because in the abdomen you may never know where the cancer comes from.

First of all, I do not favor radiation over surgery as a standard treatment of cancer of the breast. I do not support McWhirter[8] in his position that simple mastectomy plus irradiation should be used in all or even in most patients with breast carcinoma. But it is possible that the opposite position—that all operable cancers of the breast should be treated by radical mastectomy—will be proved to be just as untenable as that of never employing radical mastectomy. There may be a middle ground. If there are the equivalent of basal cell cancers in the breast, the equivalent of squamous cell cancers, the equivalent of melanomas, then any one of these may be present in any case. But we know that the breast is one location where the melanomalike cancer that spreads both to the lymph nodes and throughout the system is fairly common; in fact, it predominates. The problem is how to recognize this type of cancer, how to avoid operating on the ones in which operation may disseminate the disease.

The true significance of McWhirter's work has nothing whatsoever to do with radiation or whether radiation is better than surgery. The interesting thing is that McWhirter, as you probably know, divided his cases into three groups. In the first five year period, taking all cancer patients living in the southern part of Scotland, he applied radical mastectomy as the treatment of choice to the majority of the cases. In the second five year period, knowing the results of the first five years, he added x-ray therapy. There was not much improvement in survival rate, but he did notice a decrease in the incidence of local recurrences and he noticed that these local recurrences often could be controlled by x-ray.

If local recurrence can be controlled by x-ray, McWhirter reasoned, and if it is not local recurrence but systemic disease that kills the patients, a simpler operation should be tried and an attempt made to control local recurrences with roentgen therapy. This he did, expecting that he would have an incidence of five year survivals no different from that following radical mastectomy and roentgen therapy. But the astonishing thing was that the rate of survival was increased in the patients treated by simple mastectomy. It rose between 10 and 15 per cent at both the five and 10 year intervals. This improvement could not be attributed to the radiation, because radiation was given to all the patients in both groups. The survival rate rose as the result of *not* doing something—not dissecting the axilla. McWhirter believes this is due to the fact that in the poorly chosen cases with unfavorable cancers, axillary dissection further disseminates the disease by cutting through cancer-filled lymphatics and blood vessels. He views the lymph nodes as a barrier to the further spread of cancer and considers the function of the lymph nodes as a barrier is perhaps more important than the dissemination of the disease that might come from involved nodes.

According to this theory, a lymph node may act either as a barrier to prevent spread of cancer or, if involved, as a source of further spread of the disease. The challenge again is to determine which lymph nodes should be preserved as barriers and which should be removed as potential sources of spread. I am sure we all recognize that there are some cancers of the breasts, like the inflammatory cancers, that grow much more rapidly and make the patient much more uncomfortable when radical surgery is attempted.

Haagensen and Stout,[9] although they are

working from exactly the opposite point of view from that of McWhirter, actually are thinking along the same lines. McWhirter is emphasizing treatment with radiation, Haagensen is emphasizing radical mastectomy; but both of them are pointing out that radical operations are harmful when performed for advanced cancers. Haagensen is constantly limiting the number of cases that he considers adaptable to radical mastectomy, and is much more conservative than the average surgeon in advising such treatment. Therefore, in the selected cases in which he uses radical mastectomy his results are outstanding. McWhirter, by employing x-ray in the unfavorable cases, likewise gets good results.

It is the variability of the biologic behavior of various types of cancer that I wish to stress. This variability makes it absolutely necessary for us to find some way to recognize before operation, as we can on the skin, the difference between the various kinds of cancers and to predict which will behave like basal cell cancers, which like squamous cell cancers, and which will act like malignant melanomas. If we could predict the clinical behavior of cancers, we could select the proper treatment and improve our results.

Perhaps in some cancers we should devote less attention than in the past to the factor of time. To go back to cancer of the breast, because this is most easily understood, there is no definite correlation between the apparent duration of the tumor (based on its history) and its ultimate curability. Naturally, the postoperative survival is going to be longer in any group of patients who are operated on right at the beginning of their disease than in a group operated on after they have had signs and symptoms for four or five years. If the natural course of the disease is six years, the patient will not survive for five years after operation if he waits four years before seeking treatment. On the other hand, if the natural course of the disease is six years and operation is done in the first year the patient will be alive five years after the operation and will die in the sixth. But if you calculate the survival in the two groups from the time of the first onset of the symptoms there is no difference in the survival times. Postoperative survival is therefore not necessarily an accurate measure either of the efficacy of treatment or of the effects of delay in treatment. Survival from the time of onset is more important. This type of study suggests that often by the time the tumor has become large enough to be felt it has already metastasized. If it is capable of metastasizing systemically, it usually will have done so before it can be recognized.

There may be cancers in the breast, just as there are cancers of the head and neck, which never metastasize systemically, which remain localized in the breast and in the lymph nodes over long periods of time. These tumors certainly can be controlled by radical surgery. Operation in these cases is the best possible treatment, just as it is in cancers of the head and neck and papillary cancers of the thyroid. But to distinguish these cancers from those in which operation may disseminate the cancer is the problem.

For many years in cancer of the skin and in cancer of the exposed surfaces, we have followed the basic principle of excising the primary lesion as promptly and as widely as possible. In cancer of the lip and skin we do an adequate local operation, the width of resection depending on the type of cancer. But in the breast we do not know what kind of cancer it is. Would it be feasible to apply the same principle to cancers of the breast we do to cancers of the lip and skin? The one thing that we must be sure of is that we do an adequate local operation. Perhaps in a few months occult systemic metastasis will become evident, and, if so, the patient will have been saved all the discomfort and expense of radical mastectomy and of x-ray therapy. Perhaps three years later there will be one solitary lymph node in the axilla and then, just as in cancer of the lip, a good radical resection of the lymph node-bearing area can be done. In skin cancers where the cancer and its zone of metastasis are under observation, it has not been proved that the so-called prophylactic lymph node dissections are more effective than those performed when the metastatic disease becomes apparent. We have no proof that treatment is less effective when we remove the

primary tumor widely and then watch its zone of metastasis, and treat the metastases at a later date if they appear. Perhaps a graded approach to the treatment of some cancers other than those of the skin would be of value. Perhaps in others we should do the widest possible operation at the earliest possible moment. In either event it is certain that the initial treatment of the primary tumor must be adequate to prevent local recurrence.

These thoughts cannot be put into effect tomorrow; it is going to take long and careful study to determine which of our present treatments are valid and which require revision. Only one thing is certain: We have no reason to be self-satisfied with our present treatment of cancer.

I am making very little change in my actual cancer technics and treatments. I am taking much greater care, however, to prevent dissemination of cancer, because I view cancer as just as implantable as bacterial infection.

Finally, I think that if we all keep watching and looking at the variability of cancers in various organs and of the various cancers in the same organ, sooner or later we will be able to determine which should be treated by the most radical operation at the earliest possible date, which perhaps should not be treated at all, and which should be treated in the graded manner to which I have just referred. Variability may be the key to the most effective treatment of cancer.

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41st Annual

INTERSTATE POSTGRADUATE MEDICAL ASSEMBLY

Cleveland, Ohio, October 22-25, 1956

Eczematoid Conditions of the Hands

Eczematous and eczematoid conditions of the hands constitute one of the most common of dermatologic conditions. These disorders present many controversial aspects, especially from the standpoint of etiology and classification. The dermatoses in this group include contact dermatitis, eczematoid ringworm infections, *Streptococcus* dermatitis, nummular eczema, and allergic and pustular bacterid eruptions.

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Chronic Pulmonary Histoplasmosis

W. D. SUTLIFF AND L. L. BURKETT*

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IN 1953, in collaboration with Hughes and Ulrich,[1] we reviewed seven cases of active, chronic pulmonary histoplasmosis which had been reported in the literature, and we reported four more cases. Two reports of groups of cases have appeared subsequently,[2,3] and in one of these reports the disease was said to be a problem in tuberculosis hospitals.

Subsequent experience with 22 cases of chronic pulmonary histoplasmosis has confirmed our original impression that this type of the disease predominates in hospital practice. As a result of this additional experience, it is possible to describe certain variations in the course of the disease. In some cases, the clinical manifestations resembled those of other pulmonary diseases.

Case Reports

We shall report four cases because they are representative of the group and will serve to illustrate the course of the disease and furnish examples of the differential diagnosis.

Case 1—Chronic pulmonary histoplasmosis with fibrocavitary lesions of both lungs. A 42 year old white man, a Mississippi poultry farmer, was admitted to the hospital on September 20, 1954. During the previous two months, he had had a cough, slight pain in the anterior part of the left side of the chest, and dyspnea on exertion. He had lost 20 pounds.

W. D. SUTLIFF

L. L. BURKETT

The results of physical examination were not significant. Roentgenographic examination disclosed fibrous and nodular infiltration in the upper third of both lungs (figure 1). Planography revealed several translucent areas which appeared to represent cavities. Calcified nodules were seen in the hilar region and in both lung fields.

Three cultures of the sputum were positive

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Presented before the fortieth annual Assembly of the Interstate Postgraduate Medical Association at Milwaukee.

FIGURE 1 (case 1). Roentgenogram made two months after the onset of symptoms and showing maximal density and extent of bilateral lesions and retraction of the hilar structures toward the lesions.

FIGURE 2 (case 1). Roentgenogram made 14 months after the onset of symptoms and showing a decrease in the density of the bilateral apical lesions.

for *Histoplasma capsulatum*, and three were negative for acid-fast bacilli. The histoplasmin skin test and the Mantoux test* were both positive. A complement-fixation test with *H. capsulatum* antigen was positive with a high titer, 1:128. The sedimentation rate of the erythrocytes (Wintrobe's method) was 35 mm. in one hour. The albumin-globulin ratio of the serum was reversed, and a moderate anemia was present.

Fungicides did not have any definite effect. The patient was observed for 12 months. He became asymptomatic except for slight dyspnea which occurred as a result of exertion, and he gained 27 pounds. Cultures of the sputum became negative for *H. capsulatum*, and roentgenographic examination revealed that the lungs were becoming clear (figure 2).

Comment—In cases in which the diagnosis is made relatively early in the course of the disease, that is, while the lesions are minimal or only moderately advanced, the symptoms are mild and the lesions usually remain stable, although exacerbations and remissions occasionally occur. There is a tendency for fibrosis to occur. This was well developed in case 1, and it resulted in distortion of the entire lung and displacement of the hilar tissues toward the apex (figure 1).

Case 2—Chronic pulmonary histoplasmosis with extensive pulmonary fibrosis, emphysema, emphysematous bullae, atelectasis, adhesive pleuritis, and spontaneous pneumothorax which was recognized six years and three months after the initial occurrence of symptoms of pulmonary disease. A 61 year old white man, a Mississippi farmer, was admitted to the hospital on May 15, 1954, three days after the sudden onset of a spontaneous pneumothorax.

The first evidence of pulmonary disease had occurred six years and three months previously, that is, in February 1948. On March 15, 1948, roentgenographic examination had disclosed a minimal lesion in the apex of the left lung (figure 3). A diagnosis of cystic disease of both lungs had been made in May

*In this case and in cases 2, 3 and 4, the Mantoux test was performed with purified derivative of the tubercle bacillus by using 0.005 mg., the second test-dose strength.

1949, and the patient had been admitted to a hospital. He later had returned to work as a clerk.

In June 1953, the patient had been hospitalized for the second time, and a diagnosis of extensive pulmonary disease had been made. Loss of weight, fatigue on mild exertion, dyspnea, cough and purulent sputum had continued to occur.

On May 12, 1954, pain had occurred suddenly in the lower part of the right side of the chest, and the patient had had a smothering sensation and dyspnea. When the patient was admitted to the hospital on May 15, he was acutely ill. Severe dyspnea was evident, but cyanosis was not present. The left side of the thorax was contracted. Hyperresonance was present over the right side of the chest, and distant breath sounds were heard at the base of the right lung. Expiration was prolonged, and many rales were heard bilaterally.

Roentgenographic examination revealed a pneumothorax at the base of the right lung and dense infiltration and small radiolucent areas in the apex of this lung (figure 4). The left side of the thorax was contracted, and the heart, mediastinum and trachea were displaced to the left.

Examination of the sputum disclosed *H. capsulatum* on several occasions. A serologic test with *H. capsulatum* antigen was positive with a low titer, 1:32. The histoplasmin skin test and the Mantoux test were positive. The sedimentation rate of the erythrocytes was 39 mm. in one hour. The value for the total serum protein was elevated, and the albumin-globulin ratio for the serum was reversed.

The pneumothorax gradually disappeared and the patient became ambulant. He was dismissed from the hospital in September 1954. In February 1955, he returned to the hospital because of extreme weakness and dyspnea which occurred as a result of slight exertion. At that time, the vital capacity was 1.67 liters, or 42 per cent of normal. Antibiotics and fungicides were administered, but they apparently did not have any effect. The patient was confined to bed because of severe dyspnea which developed as a result of slight exertion.

Comment—This case report illustrates what

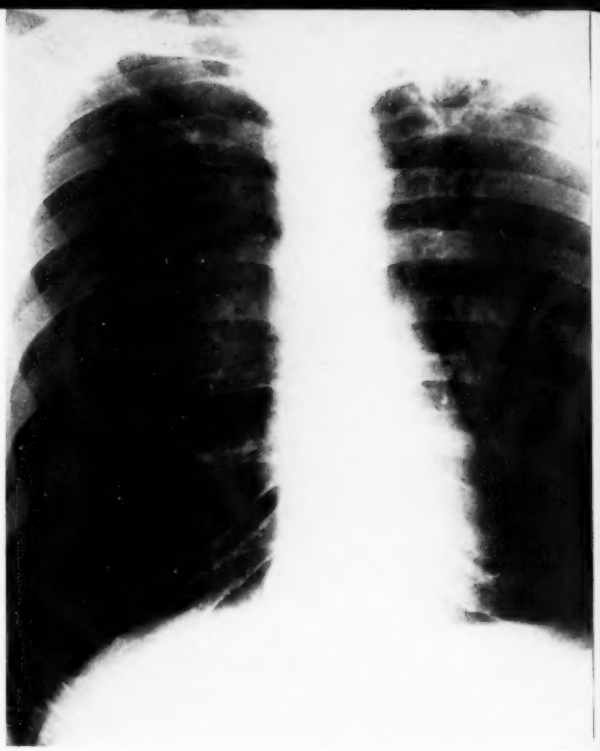
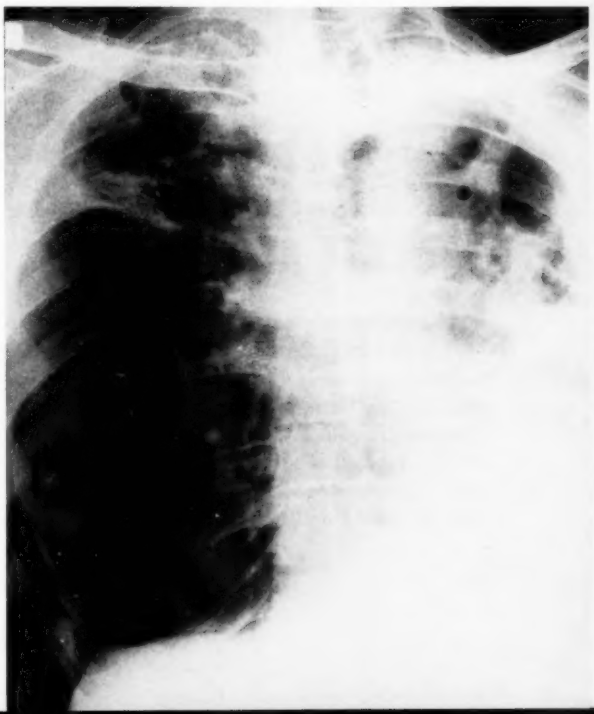


FIGURE 3 (case 2). Roentgenogram made one month after the onset of symptoms and showing minimal extent of lesion at apex of left lung.

FIGURE 4 (case 2). Roentgenogram made six years and three months after the onset of symptoms and showing maximal degree of pulmonary fibrosis, emphysema and emphysematous bullae, fibrous pleuritis and pneumothorax at the base of the right lung.



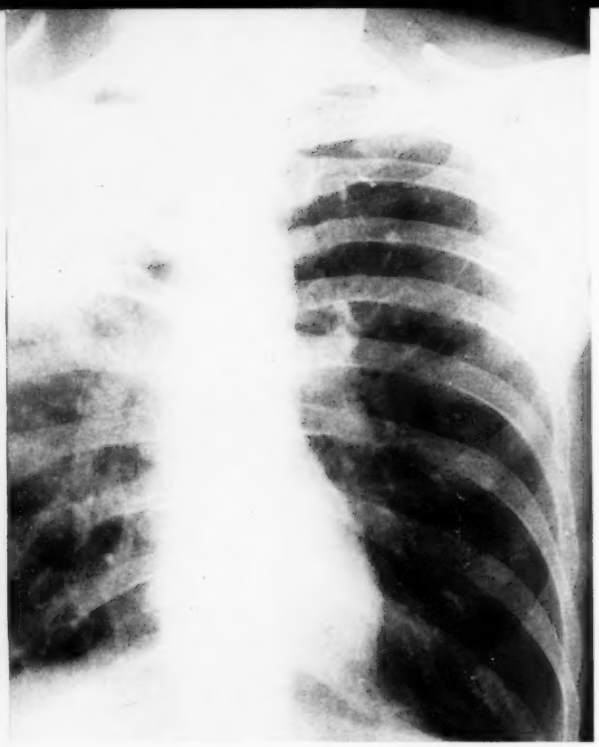


FIGURE 5 (case 3). Roentgenogram made 44 days after the onset of symptoms and showing maximal extent of the lesion in the upper part of the right lung.

appears to be a terminal condition in cases of chronic pulmonary histoplasmosis, namely, the development of pulmonary insufficiency due to extensive fibrosis, emphysema and large, thin-walled cavities. These cavities may have been due in part to the histoplasmosis and in part to the severe emphysema.

Case 3—Chronic pulmonary histoplasmosis simulating pulmonary suppuration. A 35 year old white man, a Tennessee factory worker, was admitted to the hospital on August 30, 1954, because of an illness which had begun 16 days previously. His symptoms had included generalized pain which had been most marked in the leg muscles, and malaise, fever, weakness, nausea and vomiting, and night sweats. He had lost about 10 pounds. Eighteen months previously, he had had a mild, influenzalike illness which had been followed by a persistent, productive cough.

The results of physical examination were not significant. Roentgenographic examination disclosed dense infiltration of the upper and middle portions of the right lung (figure 5). Repeated cultures of the sputum were positive for *Klebsiella pneumoniae, Staphylococcus aureus* and *Escherichia coli,* but cultures of the sputum and bronchial washings were negative for acid-fast bacilli and fungi. The sedimentation rate of the erythrocytes was 34 mm. in one hour. The histoplasmin skin test and the Mantoux test were positive. A complement-fixation test with *H. capsulatum* antigen was positive with a low titer, 1:16.

A diagnosis of chronic pulmonary infection with *K. pneumoniae* was made, and antibiotics and GANTRISIN® were administered. Fever persisted for seven days. The patient then improved symptomatically and began to gain weight. The pulmonary infiltration increased, however, in extent and density for one month, but it then decreased with the development of small radiolucent areas.

When the pulmonary lesion had persisted for five months, the upper lobe of the right lung was removed. Microscopic examination of the excised lobe disclosed the presence of granulomatous inflammation and necrosis, resembling caseation, in a large cavity and in numerous satellite tubercles. Cultures of the pulmonary tissue were positive for *H. capsulatum.*

The patient regained his strength, and his weight returned to normal. He was last seen nine months after the operation. At that time, there was no evidence of pulmonary infection.

Comment—In this case, the clinical course resembled that of pulmonary suppuration associated with cavitation and chronic infection with *K. pneumoniae,* but the findings at operation were those of chronic pulmonary histoplasmosis. It seems possible that secondary infection with pyogenic organisms may have played some part in the development of the clinical manifestations. Examination of the excised lobe would support the opinion that histoplasmosis was the chief cause of the patient's illness and that the pyogenic organisms disclosed by cultures of the sputum may, in fact, have been incidental inhabitants of the respiratory tract. No observations of the relative predominance of various pathogens were made by examination of the sputum by means

of Gram's method of staining.

The success of the operation in this case is worthy of mention. This aspect of the case will be considered by Dr. Felix Hughes and his associates who made the surgical diagnosis and performed the operation.

Case 4—Chronic pulmonary histoplasmosis with fibrocavitary lesions and chronic fibrous pleuritis. A 33 year old white man, an Alabama veteran, was admitted to the hospital on March 3, 1955, because of pulmonary symptoms which first had developed eight years previously. Fever had been the chief symptom, but the symptoms also had included a hacking cough, expectoration of sputum which occasionally had been blood-streaked, and a minimal systemic reaction.

In 1947, when the symptoms first had occurred, roentgenographic examination had disclosed an apical lesion in the left lung. At that time, a pneumothorax had been induced, and it had been maintained until 1950. Roentgenographic examination then had disclosed recent infiltration in the upper part of the right lung. In 1952, air had been injected into the peritoneal cavity, and the pneumoperitoneum had been maintained until the patient was admitted to the hospital on March 3, 1955. To the best of the patient's knowledge, examination of his sputum never had disclosed the presence of acid-fast bacilli.

When the patient was admitted to the hospital, he weighed 129.5 pounds and the left side of his chest was flat. Physical examination revealed reduction in the intensity of the breath sounds in the posterior part of the apex of the left lung, dullness at the base of the left lung, and reduced excursion of the left side of the chest. A roentgenogram of the chest was similar to one which had been made three years previously and which had disclosed calcified stippling in the upper part of each lung, deviation of the trachea to the left, and two thin-walled cavities in the upper part of the left lung (figure 6). These cavities were 5 cm. and 1 cm. in diameter respectively. The pleura surrounding the left lung was thickened to a width of 2 cm.

Microscopic examination and cultures of two specimens of the sputum disclosed *H. capsulatum*. The histoplasmin and Mantoux skin tests were positive. Complement-fixation tests with *H. capsulatum* antigen were positive, first at a low titer, 1:32, and later at a high titer, 1:128. The sedimentation rate of the erythrocytes ranged from 32 to 35 mm. in one hour. On eight occasions, a culture of the sputum was negative for acid-fast bacilli.

FIGURE 6 (case 4). Roentgenogram made five years after the onset of symptoms and showing maximal extent of lesion in the apex and pleura of the left lung. It also shows a therapeutic pneumoperitoneum.

Because of the persistence of infected cavities in the left lung and deformity of the left side of the chest, the entire upper lobe and a portion of the lower lobe of this lung were removed and decortication also was performed one month after the patient was admitted to the hospital. Microscopic examination and cultures of the excised portions of the lung disclosed *H. capsulatum*.

Antibiotics for pyogenic and tuberculous infection were administered. The postoperative convalescence was complicated by a bronchopleural fistula and localized empyema. When the patient was dismissed five months

after the operation, he did not have any acute symptoms.

Comment—This case shows that there is a marked tendency for fibrosis to develop in the lungs and pleurae, for large, thin-walled cavities to develop in the lungs, and for exacerbations and remissions to occur. It was most noteworthy, however, because the early stage of the disease resembled that of tuberculosis. If a case of this type were observed today, a diagnosis of tuberculosis would not be made unless the presence of acid-fast bacilli could be demonstrated in the sputum, but the treatment in this case was begun in 1947, when the importance of cultures of the sputum in the diagnosis of tuberculosis was not universally appreciated. It shows that the ability of a physician to recognize pulmonary histoplasmosis depends in part on his ability to rule out, or minimize, the possibility of pulmonary tuberculosis by demonstrating that tubercle bacilli are not present in the sputum.

Discussion

The four cases of chronic pulmonary histoplasmosis which we have reported were representative of the other cases of this disease which we have observed. In case 1, the diagnosis was made within two months after the appearance of definite symptoms, but the pulmonary lesions already had involved a third of both lungs, and fibrosis and retraction had distorted the structure of the remaining portion of both lungs. The course of the infection was favorable since the symptoms disappeared and the lesions became less dense during the time that the patient was in the hospital.

In case 2, the diagnosis was made late in the course of the disease. The patient was under clinical and roentgenologic observation for seven years and seven months. Extensive fibrosis, severe emphysema, large thin-walled cavities, and serious pulmonary insufficiency had developed before a diagnosis of pulmonary histoplasmosis was made. The history and previous roentgenographic examination demonstrated that the early stage of the disease was similar to that in case 1.

We wish especially to call attention to the presence of pulmonary fibrosis in the early stage of the disease in this case and to the occurrence of chronic pulmonary fibrosis and emphysema in the terminal stage. These observations in the early and late stages of the disease indicate an evolutionary course of development.

The relative importance of *H. capsulatum* and other factors in the development of the terminal clinical picture was not fully determined. This clinical picture may have been due primarily to *H. capsulatum*, it may have been the result of secondary infection that occurred after pulmonary fibrosis and emphysema were well advanced, or it may have been due to both of these causes. If *H. capsulatum* was the primary cause of the terminal clinical picture in this case, the disease may progress and serious pulmonary insufficiency may occur in the terminal stage in some cases in which chronic pulmonary histoplasmosis now is being recognized before advanced changes have occurred in the lungs. Prolonged observation in such cases should lead to more definite knowledge regarding the importance of *H. capsulatum* in producing this clinical picture.

The reports of these four cases illustrate the methods by which a diagnosis of chronic pulmonary histoplasmosis may be made. In case 1, after the possible presence of tuberculosis had been ruled out because tubercle bacilli could not be found in the sputum, the presence of histoplasmosis was promptly recognized by appropriate mycologic examination. In cases 2, 3 and 4, the initial diagnoses were chronic cystic disease of the lung, chronic *Klebsiella* infection with cavitation, and tuberculosis, respectively. In case 4, the diagnosis of tuberculosis was made without demonstration of tubercle bacilli in the sputum. The possible presence of a pulmonary neoplasm also was considered seriously in case 2. Chronic pulmonary histoplasmosis ultimately appeared to be the explanation for the clinical picture in each of these cases. The possible presence of this disease, therefore, should be considered in the differential diagnosis of tuberculosis in cases in which tubercle bacilli cannot be found in the sputum, and also in the diagnosis of chronic cystic disease of the lungs, chronic *Klebsiella* infection with cavita-

tion, as well as pulmonary neoplasm.

It is not our intention to leave the impression that chronic pulmonary histoplasmosis with the clinical picture which has just been described is the only type of pulmonary involvement resulting from *H. capsulatum* infection. In regions in which the disease is endemic, asymptomatic infection and atypical pneumonia probably outnumber other types of pulmonary histoplasmosis by a wide margin, but most of the patients with these types of the disease do not come under the observation of physicians, and very few of them are admitted to hospitals. An acute or subacute miliary type of the disease also occurs. Solitary granulomatous, nodular lesions of the lung may be due to *H. capsulatum*. Pulmonary involvement also may be part of the disseminated form of histoplasmosis in either its acute or chronic phase. The clinical manifestations of these types of pulmonary histoplasmosis differ from those which we have observed in the chronic form of the disease.

The significance of the presence of *H. capsulatum* often is obvious, particularly if other diseases can be excluded, but it usually is wise to consider the possibility of other infections, principally tuberculosis. because of its frequency, and to consider the possibility of the simultaneous occurrence of other noninfectious pulmonary diseases. In view of the increased frequency with which a diagnosis of chronic pulmonary histoplasmosis can now be made, systematic description of diseases that may simulate chronic pulmonary histoplasmosis is required.

We hope that we have pointed out some situations in which mycologic examination will prove useful. Our experience should encourage physicians with diagnostic problems in cases of pulmonary disease to add histoplasmosis to the list of infrequent but recognizable pulmonary infections. Such diagnostic efforts will add further examples of the clinical forms of this disease.

The cooperation of the following hospital services in the specific diagnosis and therapy in certain cases is gratefully acknowledged: Veterans Administration Crump Boulevard Hospital, Memphis, case 1; Pulmonary Disease Division of Veterans Administration Medical Teaching Group Hospital, Memphis, cases 2 and 3; Thoracic Surgery Section, Veterans Administration Medical Teaching Group Hospital, Memphis, cases 2, 3 and 4.

Mycologic examinations were performed by Miss E. Ulrich, M.T., Veterans Administration Medical Teaching Group Hospital, Memphis.

Serologic data were contributed by the U. S. Army Medical School Laboratory through the cooperation of Miss Charlotte Campbell, mycologist.

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MEETINGS and Postgraduate Courses

American College of Physicians: 38th Annual Session, Boston, April 8-12, 1957. Edward R. Loveland, 4200 Pine Street, Philadelphia 4, Pennsylvania, Executive Secretary.

Postgraduate courses:

Recent advances in cardiovascular diseases, Mt. Sinai Hospital, New York, October 8-12. Drs. Arthur M. Master and Charles K. Friedberg, codirectors.

Clinical neurology, Jefferson Medical College, Philadelphia, October 15-19. Dr. Bernard J. Alpers, director.

Internal medicine, Vanderbilt University School of Medicine, Nashville, October 15-19. Drs. Rudolph H. Kampmeier and Hugh J. Morgan, codirectors.

Recent advances in internal medicine, University of Washington School of Medicine, Seattle, October 22-26. Dr. Robert H. Williams, director.

Selected problems in internal medicine, University of Oklahoma School of Medicine, Oklahoma City, November 26-30. Dr. Stewart G. Wolf, Jr., director.

Gastroenterology, University of Pennsylvania Graduate School of Medicine, Philadelphia, December 3-7. Dr. Henry L. Bockus, director.

Electrocardiography, University of Utah College of Medicine and Salt Lake County General Hospital, Salt Lake City, December 3-8. Dr. Hans H. Hecht, director.

Pathologic physiology of the blood dyscrasias, Washington University School of Medicine, St. Louis, February 18-22, 1957. Drs. Carl V. Moore, William J. Harrington and Edward H. Reinhard, codirectors.

Tuition for all courses will be $30.00 for members and $60.00 for nonmembers.

Unusual Strangulating Intestinal Obstructions

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THE unusual medical problem is not only of great interest to the physician but it is also of great value to his morale. It seems certain that much of his professional zeal is derived from the anticipation of diagnosing and treating a rare medical entity.

Perhaps the rather threadbare statement that rare cases are available to every physician need not be made. A review, however, of some of the cases of acute intestinal obstruction seen at the Mayo Clinic during 1954 lends emphasis to the fact. In general, most of the cases of acute intestinal obstruction which our colleagues and we encounter are among patients who live in the immediate vicinity of the clinic, and, therefore, they are comparable in this respect to those which might be encountered at any general hospital. We are of the opinion that reports of the more unusual cases will interest the reader, and will serve to demonstrate some of our present views concerning the management of such patients.

Intestinal obstruction is seen occasionally by almost every physician. It is common knowledge that the small bowel is obstructed either by an acquired adhesive band or within the neck of an external hernial sac in at least three-fourths of the patients seen. The combination of carcinoma and obstructing diverticulitis causes colonic obstruction in the same proportion of patients. A number of factors, each of which causes not more than 2 or 3 per cent of the total cases, account for intestinal obstruction in the remaining patients.

Case Reports

Case 1—A 71 year old man came to the clinic because of severe, sharp, midabdominal pain of 20 hours' duration, and six episodes of emesia of greenish-brown fluid. No flatus had been noticed during the preceding few hours, and the patient's last bowel movement had occurred before the onset of pain. Although the pain varied in intensity, it never completely remitted. An analgesic, given to the patient before transporting him to the hospital, had

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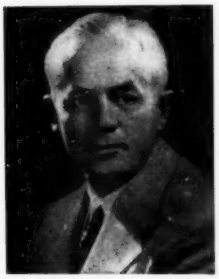
greatly alleviated his distress, however.

JAMES O. FERGESON



CHARLES W. MAYO

The patient was obese. The skin was dry and somewhat inelastic. He was afebrile. Moderate tenderness and slight rebound tenderness were present in the left upper part of the abdomen. Peristaltic sounds were active, but they were not of particularly high pitch. Abdominal distention was only minimal if present. Hernias or scars from abdominal incisions were not evident.

Preparation for definitive therapy was begun while laboratory data were being obtained. A double-lumened tube was placed in the patient's stomach, and 1 gm. of dihydrostreptomycin and 400,000 units of penicillin were injected intramuscularly. Intravenous infusion of 5 per cent glucose in normal saline solution was begun after a sample of blood was obtained for laboratory determination of serum electrolyte levels.

Urinalysis revealed nothing abnormal. Laboratory examination of the blood demonstrated mild leukocytosis, the leukocytes numbering 9700, with a differential count of 82 per cent neutrophils. Urea measured 40 mg. per 100 cc. of blood, and concentrations of chloride and bicarbonate in the serum were 95.9 and 30 mEq. per liter, respectively. Neither the serum bilirubin nor the serum amylase level was elevated above normal.

A roentgenogram of the patient's abdomen revealed a small amount of gas scattered through the small intestine. Isolated distended loops were not visible.

Symptoms seemed to indicate that the patient might have a small intestinal obstruction of obscure origin, and that it might well be of a strangulating nature. Exploration of the peritoneal cavity was elected as an emergency procedure.

A primary vertical incision was made in the right upper portion of the abdomen, and blood-tinged fluid was immediately apparent in the peritoneal cavity. Most of the small intestine was collapsed, owing to the fact that a loop of jejunum had become rotated through an arc of 180 degrees on an anteroposterior axis and had become incarcerated within a large, wide-mouthed peritoneal sac which lay just posterior to the splenic flexure and upper portion of the descending colon. The opening of the sac was continuous with the superior and inferior duodenojejunal folds of peritoneum. The mouth of the sac was so large that it was difficult to conceive that a loop of intestine could be held so securely within it. The incarcerated segment of intestine was removed without great difficulty and was derotated. Both the trapped intestinal segment and the mesentery were markedly edematous and cyanotic. A clear line of demarcation extended across the base of the mesentery between the incarcerated and free portions of bowel. However, pulsation in the mesenteric vessels seemed normal after derotation and the bowel became quite pink. It was not necessary to remove the segment.

The remainder of the small intestine was then inspected and found normal; exploration revealed no other peritoneal abnormalities. Closure of the wide mouth of the internal hernial sac was considered, but its edges were so friable that sutures would not hold in the tissue. Since the hernial sac had probably been present for a considerable time and since its mouth was so wide, further incarceration of small intestine within it seemed unlikely. The abdomen was closed without further surgical procedure.

After operation the patient did well. Antibiotics were not necessary. Gastrointestinal suction and intravenous administration of fluid were carried out for three days, being discontinued when the patient passed flatus. His diet was then rapidly advanced to one of a general nature, and he was dismissed from the hospital on the ninth postoperative day.

Comment—The treatment of this rather eld-

erly man with a left paraduodenal internal hernia seems to emphasize the importance of suspicion of strangulating intestinal obstruction even when evidence to support the diagnosis is rather meager. Severe, constant pain in the left upper part of the abdomen accompanied by nausea and vomiting is assuredly attributable at times to other pathologic conditions. Acute pancreatitis should be mentioned particularly in this regard. This patient's pain, emesia, mild leukocytosis and physical and laboratory findings could well have been caused by acute pancreatitis. Had the concentration of serum amylase been elevated, we might well have erred by attempting conservative therapy. It is our opinion that in those instances in which an acute, nonsurgical disease cannot be rather definitely diagnosed abdominal exploration should be carried out without delay, a procedure which saved this patient from a grave, and perhaps fatal, illness. The next case we present lends even more support to our attitude.

Case 2—A 56 year old farmer was admitted to the clinic with the complaint of severe, constant, nonradiating epigastric pain of 16 hours' duration. During the preceding evening, he had consumed a large quantity of beer. The pain had awakened him at 3 A.M. on the day of admission, but had subsided, only to recur three hours later. It had gradually increased in severity until it was almost unbearable. The last bowel movement had occurred 36 hours previously. Emesia of greenish fluid had occurred three times since onset of the pain.

The man was obese and in acute distress. He was afebrile. There were marked epigastric tenderness and mild tenderness to palpation over the left lower part of the abdomen, with slight rebound tenderness in both regions. Peristalsis was absent except for an occasional high-pitched tinkle.

Emergency laboratory procedures were begun while the patient was being prepared for operation, should such a measure seem urgent. A double-lumened tube was inserted into the stomach, and intravenous administration of fluid was initiated. An injection of penicillin and dihydrostreptomycin was given.

Urinalysis was negative. The leukocyte count was reported as 9400, with neutrophils numbering 93 per cent of the total. The concentration of serum amylase was not elevated.

Roentgenograms of the abdomen with the patient in both the erect and supine positions did not reveal the presence of free air or distended intestinal loops.

It was our feeling that we could not rule out the presence of a surgically treatable lesion, and surgical exploration was advised as an emergency procedure.

Through a primary right vertical midabdominal incision, we found that the mesentery of the small bowel was very mobile; its base could be delivered easily through the abdominal incision even though the patient's abdominal wall was especially thick. A loop of small intestine at the junction of the jejunum and ileum was found to be twisted on an anteroposterior axis and infarcted. After the loop was derotated, pulsation in the arteries supplying it became obvious and the color of the bowel became hyperemic. Many dark, hemorrhagic areas were present in the mesentery, however, and it seemed to us that intestinal resection might afford less risk to the patient than nonresection, because thrombosis of the veins draining the segment might easily have occurred. Accordingly, 80 cm. of small intestine was removed and intestinal continuity was restored by end to end anastomosis.

After operation, the patient did well. The double-lumened tube was removed on the fifth postoperative day, and the patient was eating a low residue diet by the ninth postoperative day. He left the hospital on the twelfth day.

Comment—This patient's age, obesity and the history of consumption of a large amount of beer immediately before the onset of the pain led us to suspect the presence of acute pancreatitis more than a surgically curable condition. The concentration of serum amylase, however, was not elevated, and we did not feel that acute gangrenous cholecystitis, acute perforation of a peptic ulcer, or strangulating intestinal obstruction could be eliminated as diagnostic possibilities. A firm stand on the necessity of surgical exploration when acute pancreatitis cannot be positively diagnosed seems necessary. As acute pancreatitis

may mimic a surgically curable intra-abdominal lesion, so may a strangulating intestinal obstruction mimic acute pancreatitis.

This case also serves to indicate a policy of surgical therapy which may be advisable in certain instances. In the past, it has usually been wise to leave unresected a segment of intestine which has been strangulated, if its color returns to normal after restoration of blood flow. It is well known, however, that venous thrombosis is likely to occur after ischemia. Now that intestinal resection can be accomplished with only small risk to the patient, the removal of a segment of mesentery in which venous thrombosis might occur seems logical. A necessary prerequisite to such a resection is the confidence of the surgeon that a safe, leak-proof anastomosis of the small intestine may be accomplished.

Since intestinal obstruction is rare in children, it is natural that the mechanism of such obstructing lesions often is rather bizarre.

Case 3—A six year old boy was admitted to the clinic in April 1954, because of severe cramping pain in the right lower part of the abdomen lasting two hours. Previously he had been perfectly healthy. The pain appeared rather suddenly, and its severity caused him to double up. Since the onset, the boy had not been completely comfortable, but the pain was markedly accentuated for approximately 30 seconds of each three or four minutes. He had vomited once since its onset. The last bowel movement had occurred on the preceding day.

The child was afebrile. Marked rigidity and tenderness to pressure with mild rebound tenderness were present in the right lower portion of the abdomen. Hyperactive bowel sounds were audible. On rectal examination considerable tenderness was present in the region of the right cul-de-sac.

Since the patient was in good physical condition and obviously had an acute condition which would necessitate abdominal operation, laboratory examination was minimal. The results of urinalysis were negative. The leukocyte count was 8000, with 70 per cent neutrophils.

A primary transverse incision was made in the right lower part of the abdomen with the use of general anesthesia. The appendix was retrocecal and normal. A large congenital peritoneal band containing a blood vessel extended from the superior aspect of the mesentery at the ileocecal junction anteriorly to the anterior abdominal wall. Twisted around this band was a loop of the terminal portion of the ileum which had become completely obstructed and contained a doughy fecal mass. At the point where the band was in contact with the ileum, the bowel was kinked and constricted by a firm scar.

The congenital band from the mesentery to the abdominal wall merely required resection. The adhesive scar constricting the ileum was removed and the bowel straightened. Appendectomy was then carried out in a routine manner, and the incision was closed.

After operation, the patient was comfortable. His first bowel movement occurred on the second day after operation, and he was dismissed from the hospital on the sixth day.

Comment—The duration of this child's illness seemed too short in relation to its severity for the diagnosis of appendicitis. An obstructing lesion was suspected preoperatively, but intussusception, a Meckel diverticulum and ileal duplication were the only obstructing mechanisms found during examination.

Perhaps the congenital peritoneal band in this case represented the remains of the omphalomesenteric artery, even though it did not lead to the umbilicus. At any rate, it serves to demonstrate that congenital bands may occur and obstruct the bowel.

Case 4—A two year old boy was brought to the hospital because of vomiting and pallor for 24 hours. His birth and development had been perfectly normal.

The child had been well on the previous morning, when he had eaten some dirt. He vomited twice, each time bringing up a large amount of dirt, after which he was anoretic. He would not arise from bed on the morning of admission, and would take only liquids by mouth. He vomited twice during the day. His mother noted the appearance of marked pallor of the child's skin during the day. The boy's last bowel movement had occurred before the onset of the illness.

The child was critically ill and in obvious shock. The pulse rate was 200 beats per minute. Respiration was rapid and shallow. The skin was pale and cool, with beads of perspiration appearing on the forehead. The eyes were sunken, with a glassy stare. The abdomen was moderately distended and exquisitely tender in all quadrants. Boardlike rigidity of the abdominal wall was present. Peristalsis was not audible. A few particles of dirt were obtained by the rectal examining finger, and the rectal temperature was 102.8° F.

Emergency examination of the blood revealed 7300 leukocytes per cubic millimeter. The differential count showed only 12 mature neutrophils, whereas 53 band forms and three metamyelocytes were seen. A roentgenogram of the abdomen demonstrated multiple dilated loops of small intestine and an indefinite radiopaque shadow in the right lower part of the abdomen that was thought to represent dirt in the cecum (figure 1).

FIGURE 1. Roentgenogram taken on patient's admission. Note evidence of dilated intestinal loops and foreign material in right lower portion of abdomen.

It was obvious that an intra-abdominal catastrophe had occurred, but the child's condition was so poor that immediate operation seemed surely fatal. A program of hydration, blood transfusion and antibiotic therapy was outlined. The child was placed in an oxygen tent. On the night of admission, 500 cc. of 5 per cent glucose in water, 100 cc. of 5 per cent glucose in normal saline solution, and 275 cc. of whole blood were administered intravenously. Tetracycline, 100 mg. every six hours, was given intravenously. Penicillin, 1,000,000 units every three hours, and dihydrostreptomycin, 1 gm. every 24 hours, were prescribed for intramuscular administration. A tube was inserted into the stomach for continuous suction.

Conservative therapy was continued as outlined for five days; daily determinations of the serum electrolyte level served as a guide for intravenous therapy. The child's general condition showed remarkable improvement. The rectal temperature stabilized at 101° F. The rigidity of the abdomen diminished greatly, and much of the tenderness disappeared, although the distention was not relieved. Marked tenderness remained over the right portion of the abdomen, and the abdominal wall overlying the right lower portion and the midportion of the abdomen gradually became reddened and edematous.

At this point, it seemed that maximal benefit had been derived from nonoperative therapy. The cause of the abdominal catastrophe was not evident. The presence of the foreign material in the intestine was thought contributory to obstruction and perforation of the bowel at some point in the right half of the peritoneal cavity.

First a small oblique incision was made in the right inguinal region, and an extraperitoneal tract was established to drain the right lower portion of the peritoneal space. When the peritoneum was opened, only a small amount of pus was encountered, and it was then obvious that no large abscess existed. A matted intestinal mass was palpable in the right upper portion of the abdomen.

A long right rectus incision was then made to allow exploration and surgical therapy. The child was found to have a large defect, or hole,

in the ileal portion of the mesentery of the small bowel. Its upper limit was at approximately the midportion of the gut, and the mesentery was again complete at a point approximately 1 ft. above the ileocecal junction. Volvulus of the ileum was present caused by a portion of the ileum which had passed through the mesenteric defect into the right upper quadrant, where it created a tight knot of intestine which had become completely gangrenous and could not be untied or derotated. Resection of the intestine had to be carried out through two gangrenous portions in order to untie the knot. After release of the volvulus and knotted intestine, it was evident that the involved portion of bowel had been supplied with blood by only a marginal artery which traversed the periphery of the mesenteric defect. The terminal ileum, which possessed a mesentery, was nevertheless devitalized by the volvulus. All of the gangrenous intestine was removed. The segment measured 105 cm. and was estimated to constitute 50 per cent of the entire small bowel.

The cecum lay high in the right upper quadrant. It was mobilized, and the lower portions of the jejunum and ascending colon were approximated in the jaws of a three-bladed clamp for exteriorization. They were brought out of the abdomen through the incision, and the wound was closed around them rapidly. A Penrose drain was brought out through the short inguinal incision.

The child's general treatment after operation remained much the same as that previously outlined. The three-bladed clamp was removed on the fifth postoperative day, and crushing clamps were applied to the spur between the colon and jejunum. Oral feeding was begun, although much necessary supplemental fluid was given intravenously. Marked edema developed in the protruding intestinal stomas, but excessive loss of fluid through the ileostomy made it necessary to close the ileocolostomy on the fourteenth day after operation. This was accomplished without particular difficulty, but, because of the edema and friability of the intestinal ends, a small Penrose drain was brought from the region near the anastomosis through a stab wound in the right upper quadrant. The abdominal wall which had surrounded the ileocolic stoma was closed with interrupted wire sutures.

After operation a small ileal fistula developed through the stab wound, and its control seems somewhat unique. Manual pressure over the fistula would cause the drainage to cease. A number of nurses, student nurses and aides volunteered to maintain manual pressure by holding a small gauze pad over the fistula at all times. After 48 hours of continuous pressure, the ileal fistula was obliterated.

The child's general condition improved slowly. Intravenously administered fluids were necessary until the twenty-ninth day of the hospitalization. Small amounts of paregoric assisted in controlling liquid stools. A high protein, high caloric diet was offered, supplemented with vitamins. On the forty-sixth day after admission, the boy was dismissed to the care of his parents at home.

During the several months that the child has been at home, his condition has improved greatly (figure 2). His appetite is good. Stools diminished to three each day. He is quite active; he plays with other children without dif-

FIGURE 2. The patient three months after operation.

ficulty, and his weight has increased from 20 to 23 lb. (9.1 to 10.4 kg.).

Comment—The primary cause of this child's obstruction was a large mesenteric defect. Rare as these defects are, they are the commonest cause of congenital obstruction of the small intestine. According to Stone,[1] almost 100 cases have been reported in the literature.

More important from the practical standpoint than the etiologic factors of the obstruction is the manner in which this case illustrates the results possible from a cooperative, concerted effort by all concerned in the treatment of children undergoing major abdominal operations. The conservative therapy was outlined by the joint effort of surgeon and pediatricians, and the fluid and electrolyte therapy was controlled by the pediatricians alone. Aside from the obvious aid given by the nurses who controlled the ileal fistula, the patient required constant care and encouragement during his entire hospitalization.

Case 5—This 62 year old housewife came to the clinic as an emergency patient because of cramping pain in the lower portion of the abdomen lasting five days. A soft, globoid hernia had been present in the right inguinal region for 20 years, but had become tenser and a little larger during her illness. She had never had an operation.

The pain appeared suddenly and was persistent. During the 24 hours immediately preceding this pain, a steady, constant pain in the right lower portion of the abdomen was superimposed on the cramping, and emesia occurred once. The patient had been constipated for a few days, but her bowels had moved 48 hours before her admission. Her oral intake had been restricted to fluids.

The patient's abdomen was tense and distended. There were exquisite tenderness and rebound tenderness in the right lower quadrant and the few audible peristaltic sounds were of exceedingly high pitch. A tense, warm, globoid hernia was present, overlying the medial portion of the right inguinal ligament. Surprisingly, it was not tender. The peritoneal cul-de-sac proved tender on digital examination of the rectum.

In the emergency only minimal laboratory examinations were carried out. Leukocytes numbered 11,900 per cubic millimeter of blood and the value for hemoglobin was 11.9 gm. per 100 cc. The results of urinalysis were negative. A roentgenogram of the abdomen demonstrated marked distention of the right portion of the colon, with the site of the obstruction in the hernia sac (figure 3).

With the conception that the patient had a "closed-loop" obstruction of the transverse colon due to incarceration in a femoral hernia, operation was advised as an emergency procedure. The necessity of both an inguinal and an abdominal incision was explained to the patient before operation because it seemed that right hemicolectomy or possibly exteriorization of the right portions of the colon and cecum might be required if cecal gangrene were discovered.

With the use of spinal anesthesia, a right inguinal incision was made, overlying the herniated mass. A large femoral hernial sac, through which dark blood-tinged fluid was visible, was exposed. Since it seemed possible

FIGURE 3. Roentgenogram taken before operation demonstrating obstruction of transverse colon in right femoral hernia.

that a segment of colon might be strangulated within the sac, a right lower rectus incision was made to allow inspection of the femoral ring from within, and, if necessary, to permit resection and removal of the strangulated segment en masse with the hernial sac. The cecum, ascending colon and a portion of the transverse colon were greatly distended, but gangrene or perforation of any portion was not evident. The peritoneal fluid did not have a foul odor. The omentum was protruding into the femoral ring and had pulled a small segment of the transverse colon with it.

The hernial sac was opened through the inguinal incision. The blood-tinged fluid was odorless. By amputating the herniated omentum, it was possible to reduce the colon back into the abdomen. A band of fibrin constricted the portion of the colon which had passed into the femoral ring, but there was no evidence of necrosis of the colonic wall.

Resection of the bowel was unnecessary, and the abdominal incision was closed. The femoral ring was closed by suturing the transversalis fascia and aponeurosis of the transversus abdominis to Cooper's ligament, and the inguinal canal was reconstructed in an overlapping manner.

The patient's postoperative course was uneventful. Her bowels moved three times on the day of operation. The use of antibiotics was thought unnecessary, but prophylactic DICUMAROL® anticoagulant therapy was carried out. She left the hospital on the tenth day after operation.

Comment—This case is presented because of its extreme rarity. Of course, femoral hernias are known to be the most commonly strangulated, but we have not been able to discover a single reported case in which the transverse colon has become obstructed in the femoral canal. Jarboe and Pratt,[2] in a study of 104 cases of strangulated femoral hernia encountered at the Mayo Clinic, found the contents of the sac to be sigmoid colon in four instances, the cecum in one case and the appendix in six cases.

Summary and Conclusions

Five cases of strangulating intestinal obstruction due to unusual causes have been presented. One man had a large paraduodenal hernia on the left side with the sac extending underneath the splenic flexure and descending colon. Another man had jejunal volvulus which apparently was due to abnormal mobility and length of the mesentery. A six year old boy had volvulus of a segment of ileum around a congenital peritoneal band, and a two year old boy had volvulus of the terminal portion of the ileum which had herniated through a large defect in the mesentery. The fifth patient, a woman, had an obstruction of the transverse colon in a large femoral hernia.

It has been mentioned previously by McKechnie and Priestley[3] that, in most instances, volvulus of the small intestine is secondary to another congenital or acquired cause. Volvulus was a contributing factor to strangulation of the small intestine in four of the five cases presented herein, but was the primary cause of obstruction in only one instance.

No fatalities occurred in the five cases reported. The treatment of each patient was in the form of individualized operation as soon as it seemed feasible; in two cases, operation was considered necessary even before the diagnosis of intestinal obstruction had been definitely established. The symptoms of each of these two patients strongly resembled the symptoms of acute pancreatitis, but surgical exploration was advised because concentrations of serum amylase were not elevated. At the Mayo Clinic, in those instances in which the diagnosis of a nonsurgical disease cannot be definitely established, abdominal exploration is favored if the patient's clinical picture might conceivably be produced by strangulating intestinal obstruction. Only strict adherence to such a policy will lower the mortality of such strangulation.

On the other hand, in cases of far-advanced intestinal strangulation with gangrene, the preoperative condition of the patient may at times be bettered from one which seems hopeless to one which can be treated surgically with success. Such restorative therapy has resulted from the use of massive doses of antibiotics via both intramuscular and intravenous routes; fluids, glucose and electrolytes introduced in-

travenously; transfusions of blood, and gastrointestinal decompression, but the factors on which restoration depends are unknown. Certainly, the length of the strangulated portion of bowel is a factor, as well as the patient's age and natural resistance. There can be no predetermined length of time for such therapy to be carried out before operation is added. In one of our cases, treatment was continued for five days before the child seemed able to withstand surgical procedures.

Intestinal resection will invariably be necessary for such patients. In other patients seen earlier, the problem of whether or not to resect the strangulated segment may not be easily solved. The risk of resection and anastomosis in such patients is not necessarily high at the present time. If the surgeon sees ecchymotic, purple areas in the mesentery which are extensive enough to cause him to think that the possibility of development of mesenteric thrombosis after operation is considerable, he may be wise to resect the mesentery and its supplied bowel, even though the bowel seems viable.

The preoperative diagnosis was not difficult in the case of the woman having obstruction of the transverse colon in a large femoral hernia because the roentgenogram of the abdomen offered considerable evidence. We have been unable to discover any report in the literature of obstruction of this portion of the colon by a femoral hernia.

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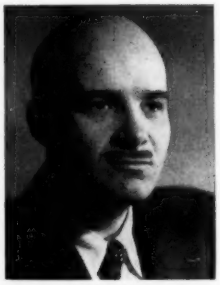

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Jaundice

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LEON SCHIFF

WHEN one sees a jaundiced patient, the problem is to determine whether the jaundice is hemolytic, hepatocellular or due to extrahepatic obstruction. Separating the hemolytic type from the other two usually is not difficult. The purpose in distinguishing between hepatocellular jaundice and jaundice due to extrahepatic obstruction, of course, is clear. The treatment of the former (hepatitis or cirrhosis of the liver, in most cases) is medical, whereas if the jaundice is due to some mechanical obstruction to the outflow of bile (usually as a result of gallstones or tumor or, less often, stricture or pancreatitis), the treatment, of course, is surgical. If a stone in the common duct and cholangitis are present the surgeon may want to elect the time of surgery, but if tumor is causing the icterus he may not want to defer operation any longer than necessary.

The clinician has four avenues of approach in solving this diagnostic problem: (1) clinical examination, (2) laboratory tests, (3) roentgenologic studies and (4) liver biopsy.

Clinical Examination

The clinical examination is the most important means of diagnosing the cause of jaundice. I shall merely touch on some of the high lights of this examination.

One should, of course, inquire as to the use of any needle for injection purposes or for the removal of a blood sample during the two to five month period immediately preceding the appearance of jaundice. Today we must all inquire as to the administration of chlorpromazine and methyltestosterone, as well as the other hepatotoxic agents which we formerly considered.

It is well known that the symptom of abdominal pain is very inconspicuous in hepatitis. The patient with this disorder feels more of a dragging sensation, usually in the epigastrium or right upper quadrant.

In cases of stone in the common duct there is typical biliary colic in most cases, but a fair

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percentage of patients, perhaps a fourth, do not have pain. This is particularly true in elderly patients in whom the clinical picture may be one of fluctuating or intermittent painless jaundice.

The pain in carcinoma of the pancreas is fairly characteristic. We owe our thanks to the late Dr. Chauffard for describing this type of pain. Usually it involves the epigastrium or left upper quadrant. It frequently radiates to the back. It is more severe when the patient lies on his back and less severe when he lies on one side or when he flexes his spine, sits up and bends forward. When you get a story of this type of pain, strongly suspect a neoplasm of the pancreas. In some cases this may be the only clue to the diagnosis and complete study may not reveal any additional findings.

Chills and fever, we all know, are very prominent in common duct stone because of the associated cholangitis. Remember, too, that they do occur in the preicteric phase of viral hepatitis, in which the chill usually is not a shaking one as it is in cholangitis. In cholangitis the chills and fever may follow the icterus; this would be most unusual in viral hepatitis.

I want to stress the clinical significance of pruritus. George Budd, the famous English clinician, emphasized more than a hundred years ago that pruritus is most commonly described by patients whose jaundice is due to tumor. That still holds. We may see considerable pruritus in biliary cirrhosis, we may see it occasionally in other forms of jaundice, but by and large when itching is prominent and persistent one should strongly suspect neoplasm as the cause of the jaundice.

I am sure you are well aware today of the importance of considering homologous serum jaundice when you see a jaundiced patient who had a gallbladder operation two to five months previously, particularly if a blood transfusion was given at the time of operation. In the past we always thought of a residual stone or a possible stricture—some complication of the biliary disease.

In the physical examination one should look for vascular spiders which usually occur above the level of the navel and which may be seen or felt to pulsate. They have a central head and small, radiating, leglike structures. They sometimes are best seen with the aid of a magnifying glass and a flashlight. By applying gentle pressure over them with a glass slide, they may be shown to pulsate. One can compress the head of the spider with the point of a pencil and thereby obliterate the lesion entirely; on releasing the pressure of the pencil point, the redness reappears. Vascular spiders occur occasionally in healthy persons. They are seen in pregnancy and also in vitamin B deficiency states, but when they appear in numbers they most commonly indicate liver disease, particularly hepatic cirrhosis.

In addition to searching for spiders, one should determine the status of the liver, the gallbladder and the spleen. One can learn much from such an examination. In hepatitis the liver may not extend below the right costal margin and may not be palpable. The same is true in cirrhosis. We believe that if a patient has had jaundice for two, three or more weeks and his jaundice is due to tumor, his liver should be palpably enlarged because it should be congested with bile, since the obstruction to biliary outflow usually is complete.

In infective hepatitis the liver is usually down one to two or two to three fingerbreadths below the right costal margin. In this disease it is unusual for the liver to extend downward four to five fingerbreadths or more; hence I make it a rule, when the liver is greatly enlarged, to consider a cause other than viral hepatitis. When the liver extends four to five fingerbreadths or more below the right costal margin, one should think of tumor, cirrhosis, fatty liver, amyloid disease or chronic passive congestion.

One should, of course, take pains to determine if the gallbladder is palpable. Remember that the gallbladder is frequently enlarged in neoplastic jaundice and the enlargement may be concealed from the palpating fingers by an overlying lobe of the liver. Thus, failure to detect a distended gallbladder at the bedside does not exclude its presence. On the other hand, if one feels a painless, distended gallbladder in a patient with jaundice, the chances are strong, as Courvoisier pointed out

years ago, that one is dealing with neoplastic jaundice. If the patient has been vomiting a good deal and not eating, the gallbladder may be distended because there has not been the normal stimulus in the form of fat to cause it to contract.

One should next determine the status of the spleen. If the spleen is palpable in a jaundiced patient (and I am, of course, excluding hemolytic jaundice), the jaundice probably is hepatocellular and one is dealing either with cirrhosis (in which splenic enlargement may be detected clinically in about half the cases) or with viral hepatitis (in which splenomegaly is present in about 15 per cent of cases). Remember that the splenic enlargement may be due to an obstructive cirrhosis secondary to biliary obstruction of some standing and hence may prove misleading.

Laboratory Tests

I would like to stress that a number of liver function tests in use are not really liver function tests, as they depend on alterations in the serum proteins which may be caused by processes other than liver diseases. The cephalin-cholesterol flocculation and thymol turbidity tests, for example, are not, in a true sense, liver function tests. The serum alkaline phosphatase determination, a very valuable test in the differential diagnosis of jaundice, is not really a liver function test. The test result may be altered from normal findings in various disorders, notably hyperparathyroidism and Paget's disease. Himsworth has well stated that there is no test that approaches in value the careful clinical appraisal of the patient, and none can be interpreted without it.

The finding of leukocytosis in a patient with jaundice rules out uncomplicated viral hepatitis. The white cell count is usually down in the preicteric phase and normal in the icteric phase of this disease. An elevated blood urea nitrogen favors Weil's disease (leptospiral jaundice) or toxic hepatitis.

While the same liver function tests are not used in all the clinics in this country, I think more and more of us are coming to use the cephalin-cholesterol flocculation, thymol turbidity, zinc sulfate turbidity, serum alkaline phosphatase, serum bilirubin and, in cases without jaundice, the BROMSULPHALEIN® excretion test. This "liver profile" is valuable in distinguishing medical from surgical jaundice.

In most cases of medical jaundice the cephalin-cholesterol flocculation test is positive, the thymol turbidity is increased, the zinc sulfate turbidity is increased, and the serum alkaline phosphatase may be elevated slightly but is usually less than 10 Bodansky units or 30 King-Armstrong units. Notice that these tests are *not invariably positive* in hepatitis. The cephalin-cholesterol flocculation test is positive in only about 80 per cent of cases.

One can differentiate common duct stone from tumor by means of these tests. The serum bilirubin is not as high in common duct stone, being usually less than 10 mg. as contrasted with a value of usually more than 10 mg. in neoplastic jaundice. The alkaline phosphatase is higher in neoplastic jaundice. The cephalin-cholesterol flocculation and thymol turbidity tests are more frequently positive in the cases of stone and cholangitis, presumably because of "secondary" hepatitis. The higher values for serum alkaline phosphatase in neoplastic jaundice may be explained by the more complete and persistent biliary obstruction.

As Cecil Watson has pointed out, the urinary urobilinogen is decreased or virtually absent in 90 per cent of cases of neoplastic jaundice and the fecal urobilinogen is similarly decreased.

I feel that we do not do biliary drainage perhaps as often as we should. It is well to remember that one may demonstrate a good many cholesterol crystals and calcium bilirubinate crystals in patients with stone, and that biliary drainage is one way of proving that obstruction is not present, particularly if you get bile.

We have not applied the Papanicolaou technic to duodenal contents, as have Lemons and Byrnes. One can demonstrate tumor cells in material so obtained.

Roentgenologic Studies

The x-ray, helpful as it is in the diagnosis of digestive tract disease, is of limited value in jaundice. (1) It cannot diagnose hepatitis

directly; (2) we do not see the tumors themselves that produce the jaundice; (3) we are limited in our use of cholecystography and intravenous cholangiography in the presence of jaundice, and (4) the visualization of gallstones on a roentgenogram does not mean that they are the cause of jaundice.

Occasionally one may be able to demonstrate both a common duct stone and a stone in the gallbladder on a plain film of the right upper quadrant of the abdomen, but this does not happen often enough.

The roentgenologic finding of esophageal varices naturally directs attention to hepatic cirrhosis. Displacement of the stomach to the left or posteriorly means there is enlargement of the liver. Anterior displacement of the stomach usually means an expanding lesion in the retroperitoneal area, under these circumstances usually in the pancreas. X-ray examination may disclose compression of the duodenum by an enlarged gallbladder due to a tumor of the common bile duct or associated with carcinoma of the head of the pancreas. Smoothening and widening of the duodenal curve mean a space-occupying lesion in that region, most commonly carcinoma of the pancreas. In carcinoma of the ampulla of Vater the descending duodenum has the configuration of a reversed 3 (Frostberg's sign), usually produced by a craterlike lesion in this area. This sign has considerable value but is not infallible. Occasionally one sees a defect in the descending duodenum in viral hepatitis, probably due to edema and inflammation in the duodenum, to duodenitis or papillitis.

You are well aware of the importance of operative cholangiograms in revealing stones that may be missed by other means. Of course, if you make several roentgenograms and see the shadow shift, you know there is something floating in the duct, and that means in all likelihood a common duct stone.

Roentgenograms reproduced in the German literature from a paper by Hornykiewytsch and Stender in the early days of intravenous cholangiography have much denser shadows than we have been able to obtain and, as far as I know, much denser than almost anyone else in this country has been able to obtain.

Liver Biopsy

Liver biopsy, as I am sure you realize, is not without risk under any circumstances, and more particularly in jaundiced patients because of the greater tendency to hemorrhage and bile peritonitis (in cases of obstructive jaundice). Therefore, one should think twice before employing needle biopsy of the liver in a jaundiced patient. Nevertheless, we believe that several indications for its use exist. The procedure is indicated when there is difficulty in distinguishing medical from surgical jaundice or when there is a history of exposure to a hepatotoxic agent. If you know, for instance, that a jaundiced patient has been exposed to carbon tetrachloride, that does not mean necessarily that the chemical produced the jaundice. We have had such cases in which we have found a viral, not a toxic, hepatitis, and we have been able to let the patient return to his occupation after his hepatitis had subsided. The same has occurred under PAS therapy for tuberculosis. Recently in such a case the hepatitis was found to be of the homologous serum variety, and it probably occurred from the use of streptomycin and not following PAS.

In the presence of an obscure systemic disorder, biopsy occasionally will reveal a granulomatous disease which had been entirely unsuspected. While a biopsy will not indicate the specificity of the disease, it may put the clinician on the right track and assist him in running down the exact nature of the disorder.

We have been surprised at the frequency with which we can demonstrate metastases in the liver by needle biopsy. In over 100 patients we have been able to do this in 75 per cent of the cases. That sounds hard to believe, but it was true in the first 50 cases in which we did the procedure, and it was equally true in the next 50. Other investigators have had similar experiences. Just imagine a small piece of liver tissue about 2 cm. long and 1 mm. wide, obtained blindly through the intercostal approach, revealing the presence of metastatic tumor in 75 per cent of cases.

Lastly, when there is hepatomegaly of undetermined origin one may have to resort to a biopsy. One may think the patient has hepa-

titis and find he has a fatty liver, or you might think he has cirrhosis and find he has a tumor, and so on.

We use the Vim-Silverman needle, and most of our specimens are obtained with the transthoracic approach.

A typical specimen obtained from a patient with viral hepatitis shows periportal infiltration (around all the portal units), evidences of intralobular infiltration, ballooning of the cells, etc. In fact, the only way we have of proving viral hepatitis today is by needle biopsy, as we do not have a serologic test or any other test to prove its presence.

In obstructive jaundice one finds bile stasis, bile plugs and sometimes bile lakes. We have never seen the latter in anything but extrahepatic obstructive jaundice.

A specimen obtained from a patient with infectious mononucleosis may show distention of the sinusoids with atypical lymphocytes. I am sure we frequently mistake infectious mononucleosis for viral hepatitis, and vice versa. It is very important to distinguish between these two conditions, because in infectious mononucleosis there is no point in giving gamma globulin for prophylactic purposes to those who have been exposed; secondly, one would not have to invoke enteric precautions. The needle biopsy may not differentiate these two conditions in the absence of sinusoidal distention.

One may find that the patient has a very fatty liver, and when these persons, particularly if they are alcoholics, get an infection they can suddenly become extremely ill and may die in 24 to 48 hours. Jaundice may be very striking in these cases.

Needle biopsy reveals the presence of tumor in most instances of metastatic neoplasm but it may not reveal the primary site. Once in a while it may lead to the detection of the primary site.

I want to describe an example of jaundice following methyltestosterone administration. It is similar to THORAZINE® jaundice. There is bile stasis around the center of the lobule and very little evidence of change in the periportal zones or elsewhere in the lobule. It is very important to recognize this form of jaundice and distinguish it from extrahepatic obstructive jaundice in order to avoid unnecessary surgery.

Dubin and Johnson have recently described a chronic idiopathic jaundice in young persons which simulates constitutional hepatic dysfunction or physiologic hyperbilirubinemia. The patients feel tired, may have a little pain, and are often mistaken for cases of viral hepatitis. The biopsy specimen in these cases shows a peculiar brownish pigment in the liver cells. The authors do not know just what it is; they think it might be a lipochrome and that the trouble is due to some metabolic defect in which the liver is unable to excrete bilirubin, Bromsulphalein, etc.

By means of the clinical examination alone, one may make the correct diagnosis of the cause of jaundice in as high as 80 per cent of the cases. Addition of the laboratory tests may increase this figure to about 90 per cent. By adding the needle biopsy in selected cases, we have reached a diagnostic efficiency of about 92 per cent. The clinician who makes a careful and complete examination, stressing some of the points I have tried to emphasize, should obtain an equally high degree of diagnostic accuracy.

AUTHOR'S CORRECTION

In the article entitled "Modern therapeutic approach to malignant hypertension," by Dr. James A. Evans, published in the June POSTGRADUATE MEDICINE, the sentence starting at the bottom of page 538 should read:

For this purpose, we administer 150 to 200 mg. of RAUDIXIN® daily, or we give *0.75 to 1.00 mg.* of SERPASIL® if anxiety and nervous tension are important factors.

Uterine Retrodisplacement: Etiology and Management

ROBERT W. KISTNER* AND CHRISTOPHER J. DUNCAN†

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THE enthusiasm for surgical correction of uterine retrodisplacement so prevalent in the last 25 years has now abated. Gynecologists, especially those trained during the last decade, generally regard the operation as of no value. Many have completed recognized residencies without having performed a single suspension of the uterus. Similarly, the use of vaginal pessaries has received no more than token consideration.

We believe that there are certain patients with a particular symptom complex who may be helped by these simple gynecologic procedures. The selection of such a patient is difficult and necessitates taking a careful history and performing a meticulous examination, since studies in large gynecologic clinics have shown that approximately 20 per cent of all women examined for gynecologic complaints have uterine retrodisplacement. In many such women the malposition of the uterus is asymptomatic and is merely of statistical interest. In others, however, marked improvement may be brought about by appreciation of a few principles of pelvic anatomy and physiology.

The purpose of this paper is to summarize the anatomy, etiology, pathologic physiology and symptomatology of uterine retrodisplacement and to suggest a therapeutic procedure for certain cases. We do not wish to re-create interest in the suspension operation, since it is well recognized that many of these procedures served no useful purpose. However, the use of pessaries should not be relegated to obscurity.

ROBERT W. KISTNER

CHRISTOPHER J. DUNCAN

Anatomy

The fibromuscular supports of the uterus include the paracervical or cardinal ligaments, the round ligaments and the uterorectosacral ligaments. There are other factors, however, of equal importance in an anatomic consideration of the etiology of the uterine retroversion. The intrinsic muscular tone of the uterus it-

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self, together with its configuration and vascular status, may be causally related. The flabby, boggy uterus associated with the syndrome of pelvic congestion is frequently posteriorly displaced. The situation may be congenital—purely a physical derangement—incorporating a short anterior vaginal wall and an upward tilting of the cervix. The lateral cervical attachments (cardinal ligaments) are the main long axis support of the cervix and uterus. Weakening of these ligaments is probably the principal cause of prolapse, although the latter is almost always associated with some degree of retrodisplacement.

The round ligaments serve a definite function in retaining the normal anterior position of the uterus, although it is doubtful that they function alone. Even in cases of severe retrodisplacement the round ligaments usually appear grossly normal. Given sufficient tension on the posterior aspect of the cervix by the uterorectosacral ligaments and normal intra-abdominal pressure on the posterior aspect of the fundus, the round ligaments aid in keeping the fundus anteflexed. Theoretically the round ligaments also function in the postpartum period of uterine involution to return the fundus to its anterior position. Similar function is presupposed after a full bladder has been emptied.

The uterorectosacral ligaments vary greatly in size, thickness and consistency, but serve a most important function in keeping the cervix directed posteriorly. When the combination of ligamentous support is deranged, either by physiologic changes such as pregnancy or pelvic congestion or by organic causes such as infection or endometriosis, retrodisplacement occurs.

Lastly, various tumors of the adnexa or bowel may displace the uterus from its normal position.

Etiology

Uterine retrodisplacement may be considered under two general categories: (1) primary retrodisplacement which is associated with congenitally deficient supporting structures and/or a short anterior vaginal wall; (2) secondary retrodisplacement brought about by childbirth, pelvic infection, endometriosis or tumors.

Primary retrodisplacement—The uterus is always retrocessed and occasionally retroverted in infancy and childhood. At puberty it usually assumes an anteverted, anteflexed attitude, but in cases where there are other stigmas of infantilism, such as a short anterior vaginal wall and short uterorectosacral ligaments, the uterus remains retroverted. Cases of incomplete ovarian descent with shortening of the infundibulopelvic ligament and posterior pull on the uterus have been described. A large group of nulliparous patients who undergo routine pelvic examinations have asymptomatic retroverted uteri, unassociated with pelvic pathology. In these women this may be a manifestation of a generalized diminution in intrinsic tissue tone as evidenced by renal and intestinal ptoses, leg and vulval varicosities, hemorrhoids, hernias and, occasionally, uterine prolapse.

Secondary retrodisplacement (ligamentous relaxation)—As previously noted, secondary uterine retroversion is commonly associated with laxity of the pelvic supporting tissue, whether due to repeated childbirth or to vascular aberrations resulting in pelvic congestion. The rigors of pelvic delivery and the puerperium probably are the leading causes of secondary retroversion. Sustained hard physical work during the pregnancy and long hours without rest or support in the erect position early in the puerperium undoubtedly are contributing factors. Repeated pregnancies may cause a change in the normal musculature with an increasing amount of vasculature, subsequent congestion and, later, fibrosis. (Congenital factors must be considered as well, since many *grande multiparae* have anteverted uteri.)

Postmenopausally this same uterine fibrosis occurs normally and results in atrophy and flaccidity. The uterus drops back and usually is found in the axis of the vagina—both anterior and posterior supports being, for the most part, inactive. The integrity of the cardinal ligaments and the pelvic diaphragm determines whether or not prolapse will occur at this stage.

Pathologic factors in retrodisplacement include endometriosis, pelvic infection and tumors. In endometriosis the uterus is not infrequently found in deep, fixed retroversion. This process, involving as it does the peritoneum of the cul-de-sac and uterorectosacral ligaments, frequently produces areas of scarring across the posterior aspect of the fundus. The rectal serosa occasionally is involved and the adnexa may be implicated, producing a fixed, tender pelvic mass. In a recent study of a large group of proved cases of pelvic endometriosis, uterine retrodisplacement was noted in 28.7 per cent.[1]

The exudate of pelvic peritonitis may be etiologic in producing fixed retrodisplacement, since pelvic contour will cause such exudates to gravitate to the posterior cul-de-sac where organization and fibrosis occur. A large pyosalpinx is occasionally found anteriorly and adherent to the uterovesical space with posterior displacement of the fundus. Postabortive, postpartum and gonorrheal infections are the major causes of such pelvic inflammation, although occasionally a ruptured appendix or diverticulum may produce the same situation.

Most adnexal tumors gravitate into the lateral pelvis or cul-de-sac and cause anterior rather than posterior displacement of the fundus. One exception to this is the dermoid cyst which frequently is found anterior to the broad ligament with the corpus posterior (Küstner's sign). Pedunculate uterine leiomyomas may reach sufficient size so that the fundus is displaced against the sacrum and may be independently palpated. Rarely, rectal carcinoma may force the cervix anteriorly with subsequent posterior displacement of the fundus.

The idea that retroversion of the uterus may be caused by falls, injuries or extensive athletic activity generally has been discarded by most gynecologists. Obviously, without a control examination prior to the accident or activity, conclusions would be hazardous.

Pathologic Physiology

Following retrodisplacement of the uterine fundus, from whatever cause, vascular changes of great importance occur. The angle of entrance and exit of the uterine vessels is distorted, producing torsion and partial venous obstruction. The ovaries and tubes are drawn into a characteristic pelvic wall prolapse attitude with increased pressure in the veins of the infundibulopelvic ligament. Laparotomy during the early puerperium has strikingly revealed these changes, showing a large, congested, mottled, purple uterus, edematous tubes and varicosities of the veins of the broad ligament. Microscopically, the veins of the myometrium are dilated and congested.

The endometrium associated with symptomatic retroversion has not been studied extensively, but Derichsweiler[2] noted edema and overfilling of the vessels of the mucosa. Taylor,[3] in his study of pelvic vascular congestion and hyperemia, examined the endometrium in 17 cases. The findings were not unusual except for three cases of chronic endometritis. The ovaries are frequently involved, cystic degeneration being noted in more than physiologic degree. Cortical fibrosis has been described. Taylor[3] noted ovarian edema and vascular engorgement with a tough, unyielding capsule. It has been suggested that long periods of congestion result in connective tissue hyperplasia of the ovarian cortex with subsequent interference with normal ovulation. In his study of 105 cases of chronic pelvic hyperemia and vascular congestion, Taylor[3] noted retroversion of appreciable degree in one-third of the cases. However, Cotte,[4] by LIPIODOL® injection, demonstrated a reduction in uterine size following suspension of an enlarged, retroverted, congested uterus, so that there is adequate evidence for believing many of the changes are due to position alone.

Symptomatology

Probably the most common symptom noted by patients with acquired retrodisplacement is sacral backache, although it should be noted at the outset that retroversion frequently causes no symptoms whatsoever. Why this should be so is not clear. Variations in pain threshold, mental tension and degrees of vascular abnormalities have been suggested as factors, but actually the physiopathology of this pain has not been adequately explained. In several series of cases of uterine retrover-

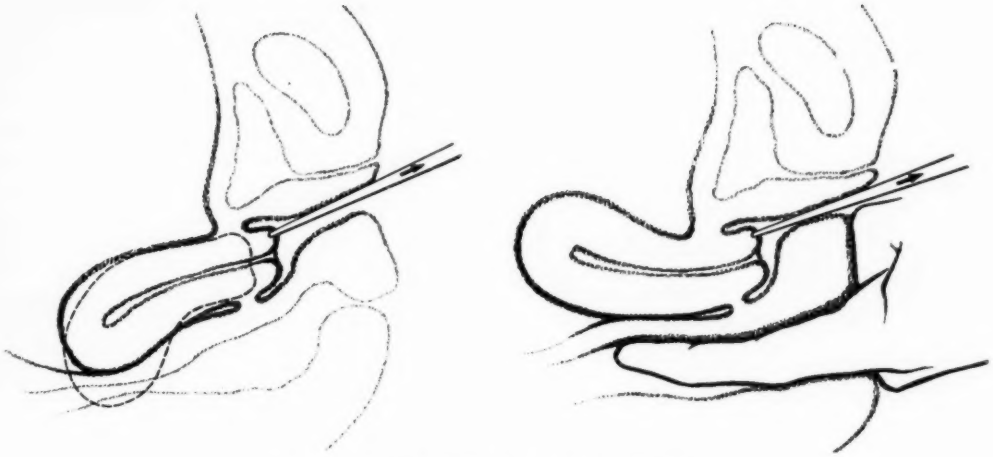


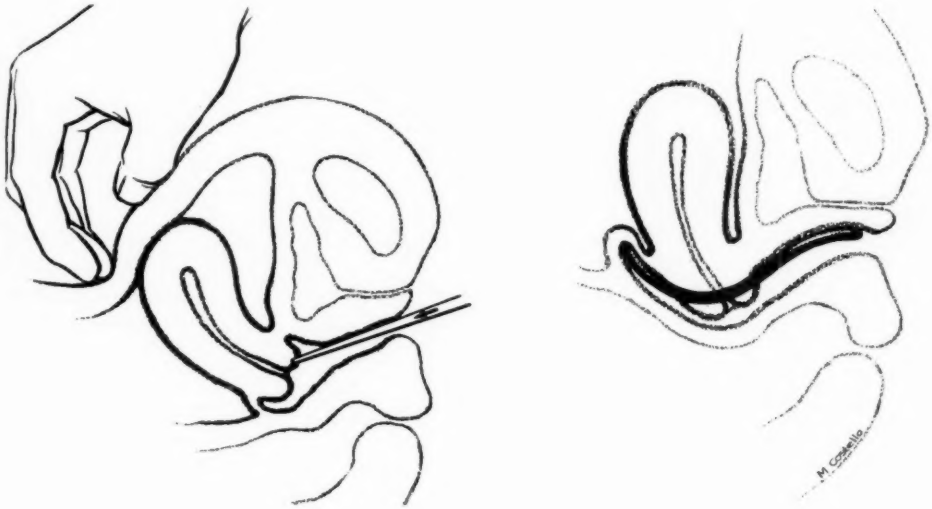
FIGURE 1. Tenaculum method of uterine reposition.

a. Dotted lines represent original uterine position. Tenaculum is placed on anterior cervical lip and traction is made as indicated by arrow. The uterus is thus pulled from its cul-de-sac position.

b. Index finger of left hand is inserted into rectum or vagina and while continuing outward traction the fundus is gently elevated.

c. As the fundus comes up, the tenaculum is thrust toward the sacrum and the right hand guides the fundus (abdominally) toward the pubis.

d. A Smith-Hodge hard rubber pessary is inserted while the uterus is held anteriorly.



sion the incidence of central, sacral backache has varied from 50 to 75 per cent. It usually is aggravated by long hours in the erect position and commonly is worse in the late afternoon and evening. A backache which is noted in the morning and which seems to improve as the patient goes about her housework probably is not caused by uterine malposition.

Many women complain of pelvic pressure or a "bearing down" feeling and are unable

to delineate their discomfort further. Occasionally lower quadrant pain is noted or the patient describes a "soreness in the ovaries." About half the patients with symptomatic retrodisplacement describe definite aggravation of their difficulties just before or at the time of the menstrual period. The premenstrual tension syndrome is commonly seen. Irregularities of menstrual flow, increased flow at time of periods with passage of clots, constipation and leukorrhea may be associated with this syndrome. The latter is often due to an untreated cervical ectropion. Retroversion has been described as an etiologic factor in abortion, and King,[5] in an analysis of a large series of cases of spontaneous abortion, found this statistically valid. Although retroversion is found in an appreciable number of cases of infertility, no conclusive evidence exists to support the idea that it is the position of the uterus which has prevented conception. The necessity for the cervix to "dip" into the seminal pool has received extensive consideration, but is apparently of minimum importance. Conception occurs whether the cervix is behind the symphysis, deep in the vault, or angulated forward or backward. As long as a film of seminal fluid with effective spermatozoa is placed across the os uteri, ascent into the uterine cavity will occur, regardless of the position or angulation of the cervix.

Treatment

At the time of pelvic examination the ease with which the retroverted uterus may be replaced usually is determined. Frequently this may be accomplished by simple bimanual examination, exerting sufficient force against the cervix to lift the fundus with the abdominal hand. If replacement is not easy, strenuous efforts should not be exerted. The presence of pelvic infection, tumors or endometriosis, of course, contraindicate further palliative measures and necessitate surgical correction. Frequently the uterus is soft and boggy and the vagina tender. In these cases patients are instructed in a course of pelvic depletion. This consists of daily, hot, 15 minute douches, sitz baths and knee-chest exercises for three or four weeks. At the end of this time replacement of the uterus usually is simplified, although occasionally it is necessary to use the tenaculum method of reposition (figure 1). In certain patients inhalation of TRILENE® may be necessary to make this office procedure painless. Should these methods prove unsuccessful, correct positioning may be accomplished by inserting a pessary and then having the patient assume the knee-chest position. In this way air opens the vagina and, by intravaginal manipulation, the uterus is replaced and a good application of the pessary is obtained. We have routinely used the Smith-Hodge or Hodge hard rubber pessary to correct retrodisplacement (figure 1d).

It is in the group of patients with so-called "married woman's complaint" that marked symptomatic improvement may be expected. Such a patient is typically a hard-working housewife of moderate parity with one or more children under four years of age. Her complaints are those of backache, heaviness in the pelvis, aching thighs, vaginal discharge, chronic fatigue and dyspareunia. Cervical cauterization may be necessary in certain cases after adequate cytologic and biopsy study. The pessary is kept in place for five to six months with monthly examination, removal and reinsertion. At the end of this time it may be removed and the patient observed for an additional two months. If symptoms recur and the fundus is again retroverted, re-treatment with a pessary may be tried. Uterine suspension occasionally may be considered, but rarely is indicated in this group of patients, or as a primary surgical procedure. It is usually performed as part of a conservative laparotomy for infertility, endometriosis or Stein-Levanthal syndrome.

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Extrapancreatic Factors in Diabetes Mellitus

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THE role of the pancreas in the endocrine control of carbohydrate metabolism is well established and needs no further elaboration in this presentation.[1] The response to administration of insulin for the treatment of diabetes, however, is not always predictable, and it becomes apparent that there are factors other than an insulin insufficiency which materially affect the patient's response to this hormone.[2] These extrapancreatic factors may be so dominant that a completely ineffectual response to insulin may result. Initially the role of the extrapancreatic factors in the induction and control of diabetes was established primarily in patients with endocrinopathies involving the pituitary or adrenal glands or both.

In the past five years the problem of extrapancreatic factors in diabetes has been significantly accentuated by the administration of exogenous endocrine preparations capable of inducing changes in carbohydrate tolerance and thereby in many cases accentuating the severity of the existing diabetes mellitus. The experimentalists such as Houssay,[3,4] Young,[5,6] de Bodo[7-9] and others[10,11] have emphasized the role of the pituitary in carbohydrate metabolism and have added much to our understanding of the interrelationship of synergism and antagonism existing between the hormones secreted by the pituitary, adrenal cortex and pancreas. Thus, Houssay showed that the diabetic state, induced by surgical ablation of the pancreas in animals, could be significantly diminished by hypophysectomy.[3,4] Young,[5,6,12] de Bodo[7-9] and others[13-16] then demonstrated the role of the pituitary growth hormone in affecting carbohydrate metabolism by decreasing glucose tolerance or actually inhibiting the action of insulin.

The clinical counterpart of the picture described by these experimentalists is apparent

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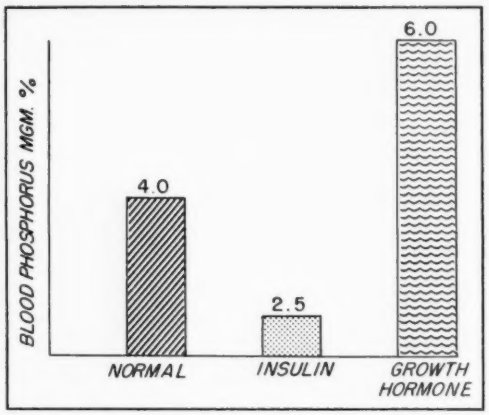

FIGURE 1. Effect of insulin and of growth hormone on blood phosphorus levels.

in a significant percentage of patients with acromegalia or gigantism.[17] Many persons with acromegalia exhibit decreased glucose tolerance. The diabetic state in these patients is usually associated with increased insulin resistance[18,19] and is accompanied by an elevation of blood phosphorus.

In all probability the elevated blood phosphorus in acromegalic patients reflects to a certain extent their disturbed carbohydrate metabolism. Blood phosphorus changes induced by growth hormone and insulin are demonstrated in figure 1 and show the diametrically opposite effects of the two hormones on phosphorus levels. While the action of growth hormone on the elevation of blood phosphorus is a recognized and interesting phenomenon, its mechanism cannot be categorically stated.[20] Elevation of blood phosphorus is not unusual in children during their growth period, and its comparable elevation in acromegalic patients has been attributed to a common denominator—namely, an increased secretion of growth hormone in both conditions.[20] Further substantiation of the role of growth hormone in elevation of blood phosphorus is demonstrated by the marked increase in serum inorganic phosphorus concentration in rats treated with growth hormones.[21]

It is interesting to speculate that since persons with active acromegalia may exhibit both insulin resistance and elevated blood phosphorus levels, the degree of elevation of blood phosphorus in acromegalia could well be a measure of the extent of insulin resistance or decrease in glucose tolerance. The effect of growth hormone in decreasing insulin responsiveness may be accomplished by inactivation of the hexokinase system by the growth hormone. Inasmuch as this enzyme is involved in blood phosphorus metabolism, it facilitates phosphorylation, a factor necessary for intracellular utilization of glucose.[22,23] Its inhibition could well result in elevation of blood phosphorus, and the level it attains might well indicate the extent of hexokinase antagonism. Insulin normally induces a decrease in blood phosphorus levels, presumably due to activation of the hexokinase system and acceleration of intracellular phosphorylation resulting in increased intracellular utilization of phosphorus.

The clinical management of the diabetic state in the acromegalic patient with insulin resistance is usually secondary to the management of the acromegalic phase itself. There is, however, the possibility that partial reversal of insulin resistance may be accomplished in acromegalia by the use of a protein anabolic agent. Androgenic substances may be helpful in these patients and may promote a more adequate control of diabetes. An acromegalic patient with insulin resistance and typical facies (frontal bossing, diastasis of the teeth of the lower jaw associated with mild prognathism) who also complained of tiredness, backaches and weakness was implanted with 450 mg. of free testosterone. Insulin resistance noted prior to pellet implantation responded to androgen therapy so that repetition of the insulin tolerance test 10 weeks after the pellet implantation revealed a comparatively normal degree of insulin responsiveness (figure 2).

In contrast to the clinical syndrome associated with enhanced secretion of endogenous growth hormone, exogenous administration of growth hormone is not of paramount clinical importance at present due to the limited availability of active extracts. These extracts, however, may result in significant elevation of blood sugar if used over long periods. Growth hormone therapy should be adequately con-

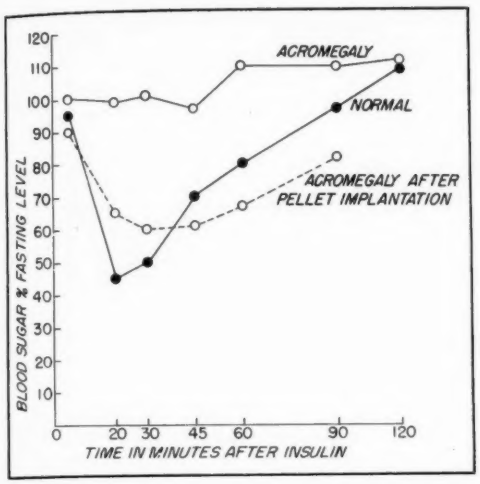

FIGURE 2. Insulin tolerance in acromegalia before and after therapy.

trolled and used with caution in patients with decreased glucose tolerance. The administration of growth hormone to patients with normal glucose tolerance also necessitates repeated determinations of blood sugar levels to ascertain whether an increase in the fasting blood sugar level has been induced as a consequence of growth hormone administration. If increase in blood sugar levels occurs, it is mandatory that growth hormone therapy be discontinued. Unfortunately, however, due to the relative scarcity of the growth hormone, only few observations on its effect on carbohydrate tolerance have been made in humans. Growth hormone administered to a series of six children resulted in an elevation of the fasting blood sugar in one child which necessitated cessation of its administration. The blood sugar of this patient returned to normal when the growth hormone injections were discontinued.

In addition to the pituitary gland, one must always consider the role of the thyroid in disturbance of carbohydrate metabolism. It was originally postulated that antagonism exists between the thyroid and pancreas.[24] This was substantiated by exogenous administration of thyroid substances. More recently it has been reported that the incidence of diabetes is twice as great among hyperthyroid individuals as in the general population, and three times more frequent among patients with adenomatous goiters.[25] The effect of the thyroid gland in decreasing glucose tolerance may be due essentially to increased absorption of carbohydrate from the gastrointestinal tract, as a result of increased phosphorylation that the thyroid hormone may achieve.[26]

The decreased carbohydrate tolerance frequently noted in hyperthyroidism may be demonstrated by performing galactose tolerance tests. Figure 3 depicts the average galactose tolerance curve in normal patients, together with those of two hyperthyroid patients and one hypothyroid person. Note the decreased galactose tolerance in patient K. F., a young male aged seven years with a diffuse, toxic hyperthyroidism associated with exophthalmos who showed all the classic symptoms of hyperthyroidism. Patient M. O. was an obese female hyperthyroid with primarily ocular signs of thyroid disease. The galactose tolerance test in these patients not only is a valuable diagnostic procedure but also demonstrates the role of the thyroid in carbohydrate metabolism. The orally ingested galactose is absorbed and can be measured directly after adequate yeast fermentation without any

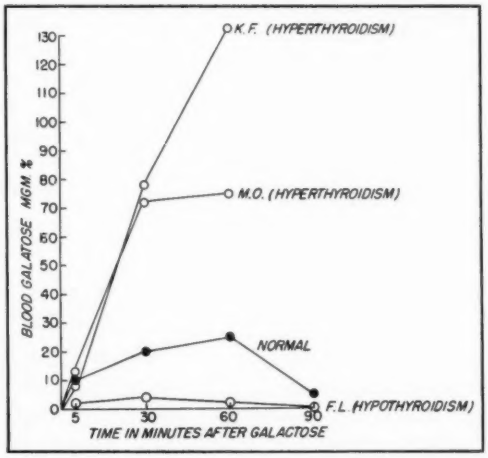

FIGURE 3. The effect of thyroid function on galactose tolerance.

interference of endogenous substances such as would occur if glucose were used in the tolerance test. The increased carbohydrate level, noted as a consequence of the enhanced absorption of the glucose or carbohydrate from the gastrointestinal tract in hyperthyroidism, increases the need for endogenous insulin. This continued increase of insulin secretion from the beta cells of the islands of Langerhans may actually result in cellular exhaustion and/or atrophy. Thus it has been shown that maintaining animals on a forced high glucose intake can result in the induction of persistent diabetes mellitus.[27] Hence the decreased glucose tolerance noted in hyperthyroidism may be due primarily to enhanced phosphorylation with the increased carbohydrate absorption followed in turn by increasing need of endogenous insulin secretion and eventually by islet cell exhaustion.

Hypothyroidism, on the other hand, is associated with increased galactose tolerance due to impaired absorption of galactose from the intestinal tract. This is well demonstrated in figure 3 by the flat galactose tolerance curve obtained during the performance of the test in a 55 year old myxedematous female (F. L.) showing the typical clinical finding of marked hypothyroidism. Administration of thyroid to patients with hypothyroidism and diabetes mellitus would be anticipated to result in further decrease in glucose tolerance and may actually accentuate the need for insulin in these patients.[28-30] Hence, cautious administration of thyroid to hypothyroid individuals who are diabetic would be wise. By and large, the administration of thyroid to the euthyroid individual does not result in sufficient changes in the thyroid status to induce elevation of blood glucose levels of any significance. Exogenous thyroid therapy would not be expected to decrease glucose tolerance in individuals with adequate pancreatic function. However, in those with inadequate islet pancreatic activity, the relative increase of absorption of carbohydrate from the gastrointestinal tract that would be anticipated following thyroid administration could result in an elevation in blood glucose not adequately covered by endogenous insulin secretion from the pancreas.[29,30] Thus the need for additional insulin in subclinical islet cell insufficiency could result in complete exhaustion of the islet cells with the residual effect of overt permanent diabetes.[30]

Adrenocortical hormones are perhaps the most important clinical endocrine factors in extrapancreatic diabetes. The role of the adrenal cortex in extrapancreatic diabetes mellitus became apparent when extracts of the adrenal cortex were first made available and when clinical entities associated with hyperfunction of the adrenal cortex were accurately characterized. Thus Cushing's disease, which can now be properly considered as a clinical portrait of excessive adrenocortical function, may be associated with a definite decrease in glucose tolerance and evidence of insulin resistance.[18,19,31] The endocrine abnormalities noted in patients with Cushing's disease and the associated carbohydrate dysfunction may be ascribed as being due to primary hyperadrenocorticoidism. Physically, the patient with Cushing's syndrome shows the characteristic effects induced by administration of excessive amounts of cortisone. These typical

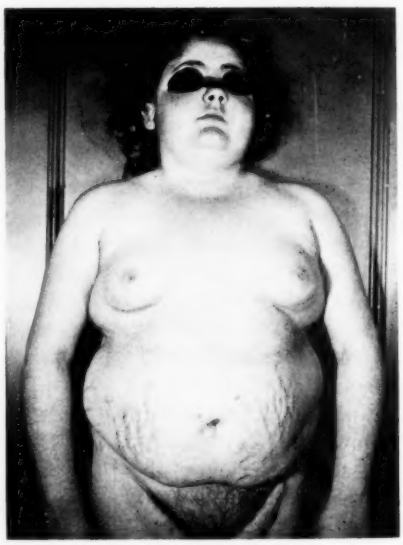

FIGURE 4. Typical physical abnormalities seen in Cushing's syndrome—"buffalo" obesity, abdominal striae, facial plethora.

physical abnormalities are exhibited by the 18 year old female patient in figure 4. She had "buffalo" obesity, abdominal striae, facial plethora and amenorrhea. This patient has shown a remarkable remission after bilateral adrenalectomy—further proof of the role of the adrenal hormones in the etiology of the syndrome.

Characteristically, most patients with Cushing's syndrome have some disturbance in carbohydrate tolerance. The classic disturbances in carbohydrate metabolism are presented in figures 5 and 6. These graphs demonstrate the decreased glucose tolerance and the insulin resistance noted in individuals with this syndrome. Since patients with Cushing's syndrome exhibit some or all of these manifestations of hyperadrenocorticoidism, it is logical to assume that their insulin resistance and/or decreased glucose tolerance can be ascribed as being due to the increased elaboration of adrenocortical hormones.

The role of the adrenal cortex in achieving these changes in carbohydrate metabolism was substantiated by the earlier studies of many investigators. They showed that the administration of aqueous or lipid adrenocortical extracts in adequate amounts was capable of inducing disturbances in carbohydrate tolerance, characterized by insulin resistance and a decrease in glucose tolerance.[32,33] The primary effect of the adrenocortical extracts in inducing these changes was attributed in part to the gluconeogenesis, presumably due to the protein catabolism induced by these extracts.[32] More recently it has been claimed that ACTH and/or cortisone directly or indirectly will decrease the activity of the hexokinase system and so decrease the ability of insulin to phosphorylate glucose.[22,23] This results in interference with the utilization of glucose by the cell and manifestly induces decreased glucose tolerance and insulin resistance. On the other hand, insulin is concerned with activation of the hexokinase system, thereby enhancing phosphorylation. Phosphorylation is followed by a decrease in blood phosphorus levels accompanied by utilization of glucose by the cell. It is conceivable that the adrenocortical preparations, while having no direct effect on

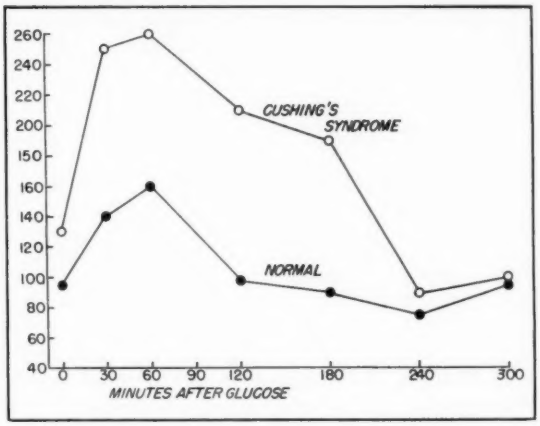

FIGURE 5. Glucose tolerance in Cushing's syndrome.

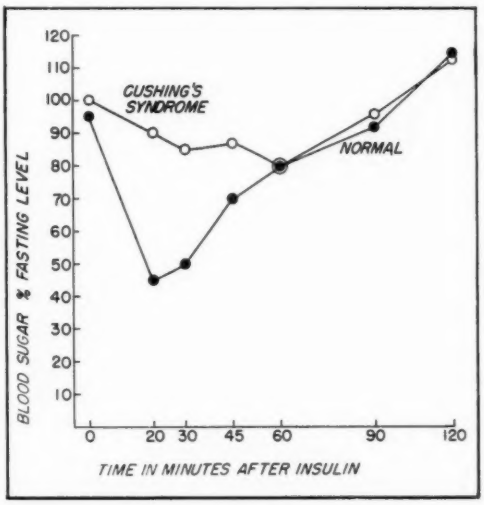

FIGURE 6. Insulin tolerance in Cushing's syndrome.

insulin per se, compete with the latter compound for the hexokinase system and secondarily induce a decrease in glucose tolerance or enhance insulin resistance, or both.

The clinical importance of these observations lies in the fact that there is an ever-increasing demand for the use of cortisone or cortisonelike derivatives in medicine at present. Numerous investigators[34-37] and our group[38-40] have shown that ACTH and corti-

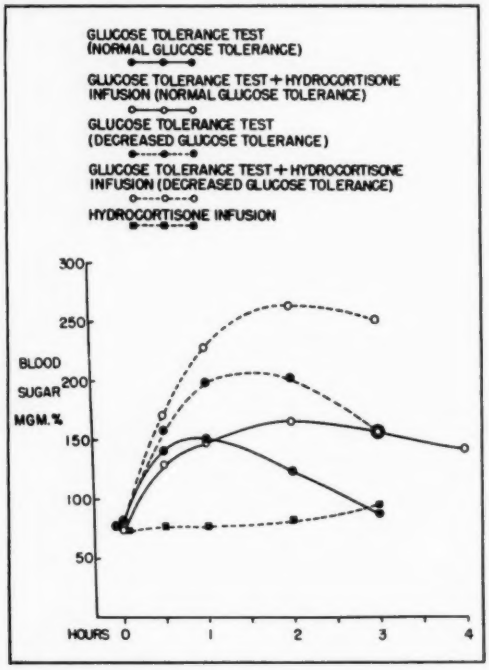

FIGURE 7. Effect of hydrocortisone infusion on carbohydrate metabolism in patients with normal and decreased glucose tolerance.

sone are both capable of decreasing glucose tolerance when administered in therapeutic doses. One can anticipate that administration of cortisone to patients who are particularly susceptible to its carbohydrate effect or to those with frank or subclinical impairment of glucose tolerance would result in further adverse accentuation of the altered carbohydrate tolerance.

There are some rather interesting aspects to this problem which we have been able to demonstrate and which are worthy of note. Intravenous administration of 100 mg. of hydrocortisone by infusion over a four hour period resulted in significant decrease in glucose tolerance both in patients with normal and in those with decreased glucose tolerance (figure 7). All patients were hospitalized and had been on an adequate carbohydrate intake prior to the experimental procedure. Glucose tolerance was measured by oral administration of a 100 gm. glucose load. Usually these patients were then subjected to the three procedures; i.e., glucose tolerance alone, hydrocortisone (100 mg.) infusion for four hours, and finally a combined hydrocortisone infu-

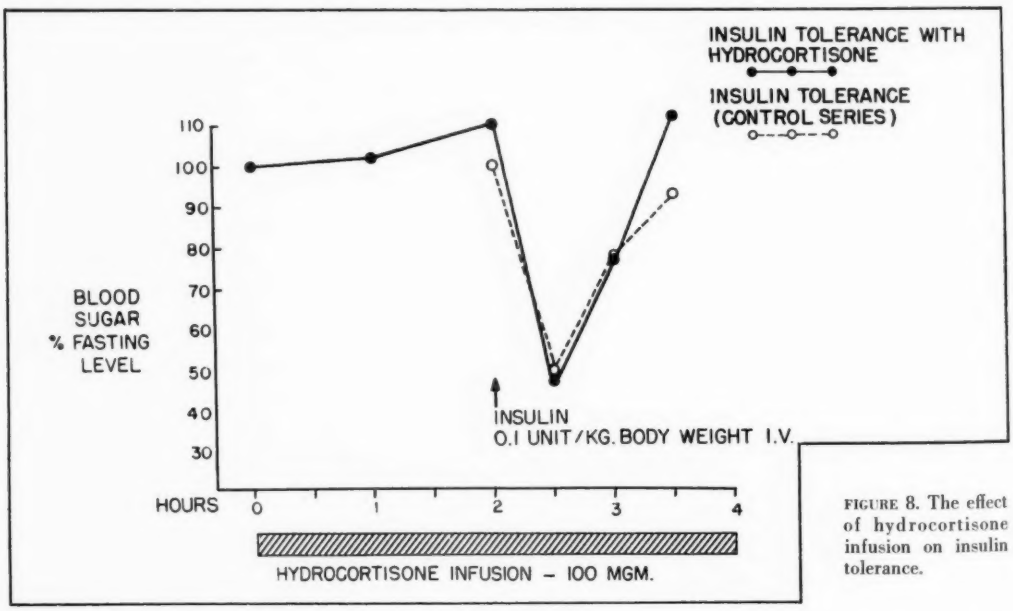

FIGURE 8. The effect of hydrocortisone infusion on insulin tolerance.

sion and glucose tolerance with the 100 gm. of glucose being administered at the initiation of the hydrocortisone infusion. The patients with decreased glucose tolerance were a group of rheumatoid arthritics who had normal fasting blood sugars.

In contrast to the studies on glucose tolerance, we failed to demonstrate any evidence of insulin resistance when 0.1 unit of regular insulin per kilogram of body weight was injected intravenously during the hydrocortisone infusion (figure 8). Insulin responsiveness, while not maximum with this dose of insulin, was comparable in the patients receiving the hydrocortisone infusion and in the normal control patients (figure 8). Insulin was administered after the infusion had been in effect for two hours, a time when significant drop in blood eosinophils had occurred[39, 40] and when noticeable effect on glucose tolerance had been achieved (figure 7). Hence the insulin must be considered as having been administered at the time of significant hydrocortisone effect.

This paradox of decreased glucose tolerance and normal insulin responsiveness cannot be explained on the basis of known actions of hydrocortisone. One possibility to be considered is that hydrocortisone actually may induce a release of an anti-insulin factor, particularly the hyperglycemic factor from the alpha cells of the pancreatic islets. The fact that decreased glucose tolerance was achieved without evidence of insulin resistance could be explained on the release of this hyperglycemic factor[41, 42] (glucagon) which facilitates glycogenolysis with the release of glucose into the blood stream. Hence, stimulation of the endogenous release of glucagon by hydrocortisone together with the addition of a glucose load can well result in excessive blood sugar levels so that a decrease in glucose tolerance due to the added glucose load is obtained. Since the hyperglycemic factor plays no role in the response of the organism to insulin, normal insulin responsiveness is still achieved during the hydrocortisone infusion.

Another possibility that should be considered as a factor in the paradox of achieving decreased glucose tolerance without affecting responsiveness to insulin after the intravenous infusion of hydrocortisone is that the hydro-

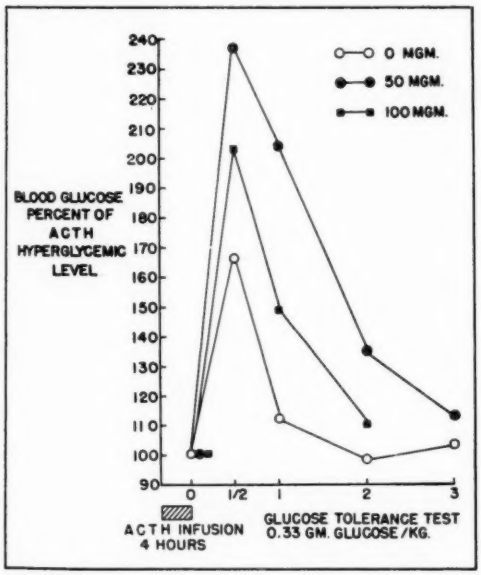

FIGURE 9. Effect of ACTH infusion on glucose tolerance.

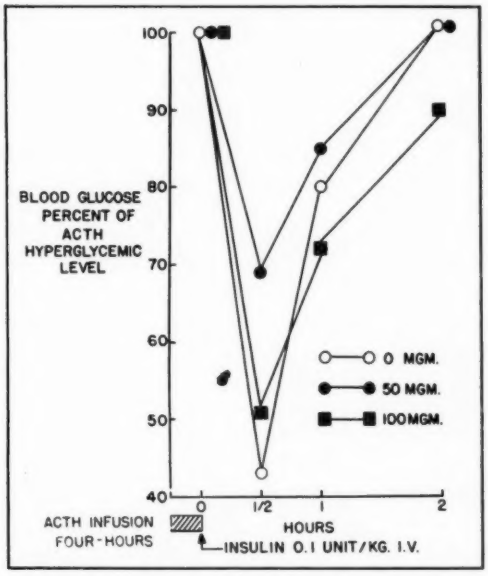

FIGURE 10. Effect of ACTH infusion on insulin tolerance.

cortisone prevents a release of insulin from the pancreas. Administration of hydrocortisone intravenously to patients subject to alimentary hyperglycemia, where normally an increased release of insulin would be anticipated, may prevent the release of insulin from occurring and thereby cause a decrease in glucose tolerance. However, since only the release of insulin is affected and not its activity, when exogenous insulin is administered a normal insulin responsiveness is observed despite the fact that the intravenously administered hydrocortisone decreased glucose tolerance.

Intravenous administration of ACTH at various dose levels has also resulted in decreased glucose tolerance.[34-36,38] The effect of different extracts, however, may be variable—some being more active in their ability to produce decreased glucose tolerance than others.[38] In contrast to the data on hydrocortisone, it was interesting to note that, associated with a decrease in glucose tolerance (figures 9 and 10), intravenous administration of ACTH also induced some measure of insulin resistance. An optimum level of insulin resistance or decreased glucose tolerance was noted with increasing doses of ACTH. When the critical dose of ACTH was exceeded, and despite administration of higher doses of ACTH, a lesser effect on glucose tolerance and insulin resistance was noted. These results are in line with the data on hydrocortisone and indicate that accentuation of the degree of decreased glucose tolerance or insulin resistance was not observed with progressive increase in the dose of ACTH. The observation has been repeatedly recorded that at times a marked increase in amount of ACTH or corticoid may mask or diminish some of its undesirable side effects on carbohydrate metabolism and/or water and electrolyte metabolism.

Not all adrenocortical extracts or steroids are effective in altering carbohydrate metabolism. There are many newer derivatives now available and some comment as to their comparative activity would be advisable. First, cortisone and hydrocortisone can be considered as being comparable in their effect on carbohydrate metabolism except that on the weight basis hydrocortisone perhaps is some 25 per cent more active. Aldosterone and 9-A-fluorohydrocortisone, two newer corticoid preparations, have a pronounced effect on water and electrolyte metabolism but in therapeutic doses have little effect on carbohydrate activity. The latter compound, in addition, has a pronounced antiphlogistic effect. Intravenously infused hydrocortisone can be expected to decrease glucose tolerance but exhibit no marked effect on the fasting blood glucose level in patients with normal glucose tolerance. However, preliminary studies with a water-soluble derivative of hydrocortisone (hemi-succinate) administered intravenously failed to result in any decrease in glucose tolerance.[43] The effect of prednisone on carbohydrate tolerance in therapeutic doses has not been characterized to date.

Summary

Extrapancreatic factors decreasing glucose tolerance have been considered. The role of pituitary, thyroid and adrenal glands in affecting carbohydrate tolerance has been discussed from the point of view of clinical entities and the factor of hormone therapy. Inasmuch as adrenocortical steroids influencing carbohydrate tolerance are in widespread use at present, the possible mechanism of their action on both glucose tolerance and insulin resistance is discussed.

ACKNOWLEDGEMENTS

The experimental data presented herein were obtained from investigations supported by grants-in-aid from The Upjohn Company and the Schering Corporation. The hydrocortisone and ACTH were kindly supplied by Dr. H. F. Hailman of The Upjohn Company. The testosterone pellets were made available through the courtesy of Dr. Norman Heminway, Division of Clinical Investigation, Schering Corporation.

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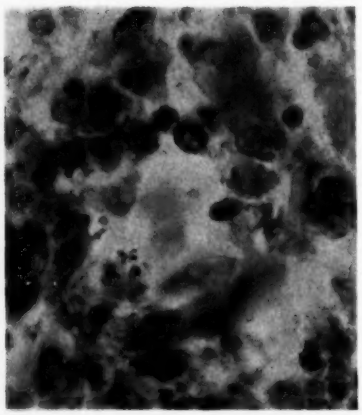
LIPOSARCOMA OF BREAST



Photographs by Z. A. Zielinski; Case Report by A. N. Cuthbertson, M.D.

Department of Surgery, Royal Alexandra Hospital, Edmonton, Alberta, Canada

THE patient, a 35 year old white woman, was first seen in May 1955, when she complained of headache and pain in her jaws and neck. During physical examination a diffuse enlargement of the right breast was found. The right breast was twice the size of the left and was firm, warm and bluish in color. The patient said her breast had been increasing in size for four months.

The patient was admitted to the hospital and a biopsy was performed. The specimen revealed the presence of a liposarcoma. Radical mastectomy was carried out.

In June 1955, the patient complained of headache and pain in her elbow, shoulder, hip and knee joints. Roentgenograms of these areas disclosed osteolytic lesions in the skull, scapulae, mandible and pelvis. A course of radiotherapy and TEM (triethylene melamine) was administered. She improved and was discharged from the hospital at the end of August 1955. She was readmitted October 31, 1955, and died 10 days later.

The Papulosquamous Skin Conditions: Their Diagnosis and Treatment

STURE A. M. JOHNSON*

University of Wisconsin Medical School, Madison

SOME 10 skin diseases belong to the papulosquamous group, but time will permit my reviewing only a few of them. Fortunately, they are easily diagnosed if one pays attention to certain details.

Psoriasis

Diagnosis—Psoriasis may mimic many other skin conditions, and for this reason I have told my students that if you know psoriasis and all its manifestations everything in dermatology shall come unto you.

Psoriatic lesions most frequently involve the elbows and knees, but may affect the scalp, genitalia and other body surfaces secondarily. They are sharply outlined, have a dull, red-brown color, and exhibit dry, shiny, micalike scales (table 1 and figure 1). Seasonal variation is the usual finding, with most patients experiencing some clearing in the summer months.

STURE A. M. JOHNSON

I am reminded of an experience during a visit to a certain clinic when I was asked to see a particular patient. I walked in, and there was a lady on a stretcher with a sheet over her. I looked at her, backed away a little, and she said, "What's the matter, doctor?"

I said, "You really have psoriasis."

She asked, "What would you do if you had it, doctor?"

"I would go to Texas," I replied.

"That's exactly where I came from," she answered.

This story emphasizes that some patients

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Presented before the fortieth annual Assembly of the Interstate Postgraduate Medical Association at Milwaukee.

TABLE 1

DIAGNOSIS AND TREATMENT OF PSORIASIS

Diagnosis

Dry, shiny, silvery scale
Affects elbows and knees; scalp, nails and torso secondarily
Dull, red-brown lesions
Sharply outlined areas
Seasonal variation
Familial incidence
Possible arthritis
Biopsy helpful

Treatment

1. Crude coal tar, 5 to 10 per cent, and ultraviolet light
2. Ammoniated mercury, 5 to 10 per cent, with 3 to 5 per cent salicylic acid, for scalp lesions
3. Anthralin, 0.10 to 1 per cent, with 3 per cent salicylic acid
4. Arsenic (Fowler's solution)
5. X-ray for stubborn patches
6. Control obesity
7. Gelatin for nails
8. Remove foci of infection

with psoriasis, about 10 to 15 per cent, are not helped by sunshine, while the rest are.

Do not forget the possibility of arthritis in association with psoriasis, the so-called arthropathia psoriatica. Remember also that one often finds a family history of the condition.

Oral lesions never occur in psoriasis. It is a disease of the extensor surfaces, primarily the elbows and knees. The histologic findings are characteristic, and a biopsy will help establish the diagnosis.

Treatment—Results of therapy are fair in psoriasis, and control of the disease may be all that one can attain. Relapses are characteristic. The treatment of choice is 5 to 10 per cent crude coal tar in VASELINE® applied to the skin and allowed to remain for 24 hours (table 1). The excess crude coal tar is then removed, and an erythema dose of ultraviolet light is given. The patient is bathed, the ointment is reapplied and ultraviolet is readministered 24 hours later. We ordinarily expect

FIGURE 1. Note the dry, plasterlike scaling on the tibial surfaces in this case of psoriasis.

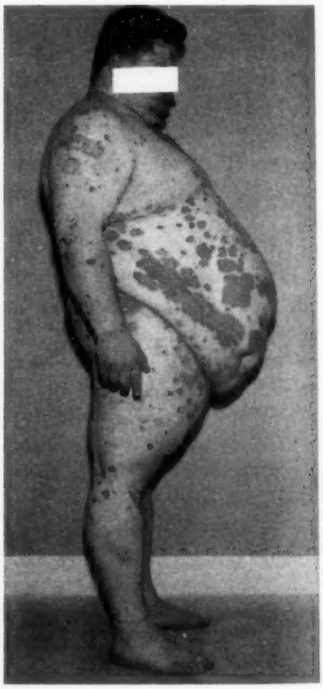

FIGURE 2. A 300 lb. man with psoriasis. Obesity seems to be a factor which adversely affects this disease.

that with this daily treatment it will take two or three weeks to clear the lesions in the average case. However, the possibility of recurrence is always present.

For psoriasis of the scalp we use 5 to 10 per cent ammoniated mercury with 3 to 5 per cent salicylic acid in Vaseline.

ANTHRALIN®, a substance similar to chrysarobin, is used in treating ambulatory patients, in strengths of 0.10 to 1 per cent with 3 per cent salicylic acid. This drug causes pigmentation of the skin similar to that seen with use of chrysarobin.

Fowler's solution has proved an excellent agent in treatment of psoriasis. Of course, excessive amounts of arsenic may produce pigmentation on the body and keratoses on hands and feet which may become malignant, and careful control of the amount used is therefore necessary.

Control of obesity is an important part of treatment. I believe that obese patients with psoriasis are more disturbed and uncomfortable than those of normal weight (figure 2).

Use of gelatin has helped patients with psoriasis of the nails. Ordinarily we prescribe an envelope of Knox gelatin per day added to fruit juice or water. If improvement is going to occur with use of this agent, it usually requires some six to eight weeks.

Removal of foci of infection is indicated. I do not mean to leave you with the impression that psoriasis is due to infection, but inasmuch as we are dealing with a disease of unknown etiology anything abnormal should be treated.

The first of three patients I shall present has had psoriasis for at least eight years. In the past few years it has become exfoliative and more extensive, and now covers the greater part of his body. His condition demonstrates certain important details in diagnosing psoriasis, one of them being the sharply outlined lesions. However, there are some unusual findings. For instance, his face is involved. When psoriasis affects the face one has to think of the possibility of lupus erythematosus or seborrhea. His fingernails are also involved, with marked pitting, thickening and subungual debris. With these changes one must consider a ringworm infection of the nail or lichen planus. This man has had arthritis, but there is no family history of psoriasis. Contrary to the usual course of the disease, he has not experienced clearing of the lesions in the summer; he states that he is no better in summer than in winter.

He has received the usual types of therapy, including crude coal tar ointment and ultraviolet light. Crude coal tar seems to intensify the itching in his case, and the superficial exfoliation is made worse by the use of ultraviolet. There has been marked pruritus, as evidenced by the excoriations.

TABLE 2

DIAGNOSIS AND TREATMENT OF DISCOID LUPUS ERYTHEMATOSUS

Diagnosis

Follicular plugging, suggesting comedones
Adherent scale, "carpet tacking"
Atrophy, telangiectasia on areas exposed to sun
Patchy scalp baldness
Laboratory studies negative except for frequent false positive serologic tests for syphilis
May be forerunner of lupus erythematosus disseminatus
Aggravated by ultraviolet light, sun and infection
Biopsy important

Treatment

1. Atabrine, 100 mg. one to three times daily
2. Chloroquine (Aralen), 250 mg. one to three times daily
3. Sun screens, such as A-fil
4. Remove foci of infection
5. Protect hands and feet from cold
6. Rest and supportive therapy

Discoid Lupus Erythematosus

Diagnosis—Table 2 summarizes the findings in discoid lupus erythematosus, as well as the recommended treatment. The follicular plugging found in this condition is suggestive of comedo formation. There is an adherent scale which can be picked off, and one finds, on turning the removed scale upside down, that the crust extends down into the follicles and that it has projections which look like spilled carpet tacks.

In addition to lesions on the face, neck,

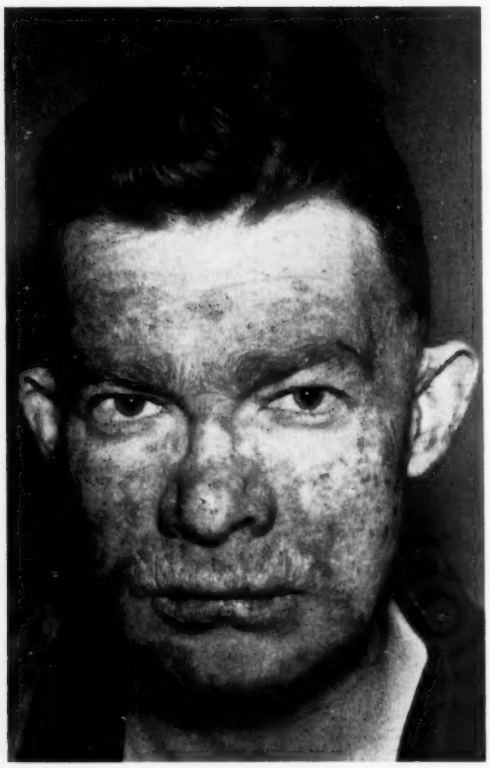

FIGURE 3. Discoid lupus erythematosus. Note the marked involvement of the lips. This patient has red hair.

hands and arms, discoid lupus erythematosus may also involve the mouth, and for this reason one should always inspect this area. A biopsy is important in diagnosis.

We know that exposure to sun and ultraviolet light will make any type of lupus erythematosus worse. Unfortunately, some of these patients are given ultraviolet light for an undiagnosed skin disorder with fatal or nearly fatal results. Atrophy and telangiectasia are characteristic findings in areas exposed to the sun. Patchy premature baldness may occur in lupus erythematosus.

Results of laboratory studies usually are negative in discoid lupus erythematosus. Some patients may have false positive serologic tests for syphilis. When one encounters a positive serologic test for syphilis in a patient with a negative history of the disease, one must seriously consider the possibility of lupus erythematosus.

The discoid variety of the disease may be the forerunner of lupus erythematosus disseminatus, and therefore it is important to employ drugs and sun protectants at all times.

Treatment—One may employ one of several medicaments in treating discoid lupus erythematosus. Many lesions will involute within three weeks following the use of 200 to 300 mg. of ATABRINE® per day. Because of

FIGURE 4. Discoid lupus erythematosus, showing the adherent scale. Atrophy and scarring will develop here with any treatment that might be employed.

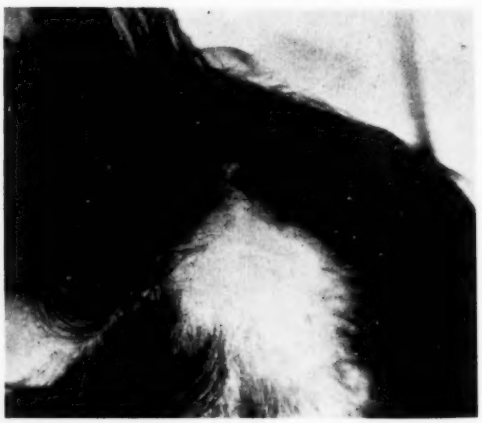

FIGURE 5. The type of alopecia that may occur in discoid lupus erythematosus, resembling alopecia areata.

side effects, such as yellowing of the skin, some patients will request other types of medication. Chloroquine (ARALEN®), 250 mg. two or three times a day, helps many patients. When control is obtained with either drug, the maintenance dose should be established. Use of chloroquine may cause loss of weight and appetite.

Many types of sun screens are available to protect against the harmful effects of exposure to the sun. A-fil is one such product.

The Raynaud-like symptoms should receive attention. Proper medication is indicated for the spastic blood vessels, and protection from cold is important so that gangrene does not occur.

Rest and supportive therapy are important for patients with either discoid or disseminated lupus erythematosus.

It has frequently been stated that red-haired and blond persons are much more susceptible to this skin disorder than are brunets. The patient with discoid lupus erythematosus shown in figure 3 has red hair. Note that the lips are markedly involved.

Figure 4 illustrates the discoid type of lupus erythematosus more clearly. The adherent scale will show, on removal, the so-called "carpet tacking." The patient in figure 4 will have atrophy and scarring with any treatment that might be employed.

The type of alopecia that may occur in this condition is illustrated in figure 5. Note the resemblance to alopecia areata. In alopecia areata the presence of exclamation-point hairs is noted, and in discoid lupus erythematosus there will be erythema, atrophy and follicular plugging.

We have a patient here who has discoid lupus erythematosus. The lesions involve his face and the V of his neck, but his hands and arms are unaffected. He has received many forms of treatment, including gold, bismuth, Atabrine and chloroquine. He believes that chloroquine has done more for him than any other therapy. He has marked depigmentation in the affected areas, and this may be due to the use of dry ice, phenol or trichloroacetic acid, or to natural scarring and healing.

A patch of discoid lupus erythematosus is present on his scalp. When this occurs, atrophy and permanent baldness are the sequelae. Alopecia areata and secondary syphilis would have to be considered in a differential diagnosis. This man's laboratory findings, including serologic tests for syphilis, are negative.

I wish to emphasize the Raynaud-like symptoms of which this man complains. His toes easily become very cold and blanched. When a patient complains of cold toes and cold fingers, think of the possibility of discoid or systemic lupus erythematosus. This patient has exposed himself to the sun more than is desirable, if the tanning which is present can be interpreted as being a sun tan.

Lichen Planus

Diagnosis—Ordinarily we think of lichen planus as a flexor disease, in contrast to psoriasis which affects the extensor surfaces. Also, lichen planus does not have seasonal variations. It characteristically appears as flat-topped, violaceous to purple-red lesions with silvery, glistening surfaces (table 3). The photograph in figure 6 shows the marked sheen. If one rotates the skin surface so that the light falls on it at an angle, there is a suggestion of multiple small mirrors attached to

TABLE 3

DIAGNOSIS AND TREATMENT OF LICHEN PLANUS

Diagnosis

Purple, red-violet color
Flat-topped, annular lesions
Silvery, glistening surfaces
Pigmentation on involution of lesions
Lacelike oral lesions
Annular lesions, genitalia
Very thin scale
Emotional factors, drugs like Atabrine
Biopsy

Treatment

1. X-ray treatment
2. Protiodide mercury, ¼ gr. three times a day
3. Bismuth (Bistrimate)
4. Wright's Liquor Carbonis Detergens and Nivea oil baths
5. Arsenic (Fowler's solution)
6. Antipruritic remedies
7. Sedation (phenobarbital or Serpasil)

FIGURE 6. Lichen planus on the foot. This photograph illustrates the marked sheen characteristic of these lesions.

FIGURE 7. Lichen planus involving the mouth, showing the lacelike network.

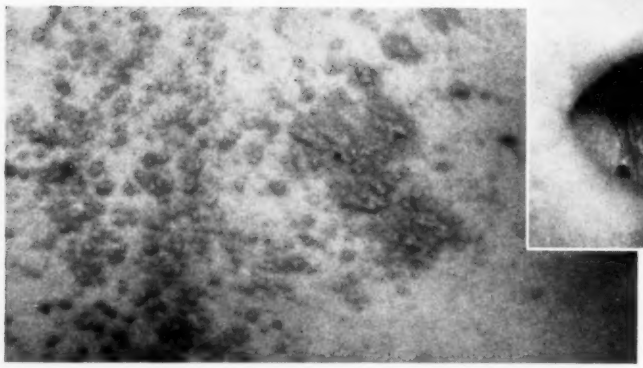

FIGURE 8. Flat-topped lesions and silvery, glistening surface of lichen planus.

the skin. A biopsy will help establish the diagnosis.

Lichen planus frequently involves the mouth, and the lacelike network of the buccal mucosa is characteristic enough to help differentiate the condition from discoid lupus erythematosus, leukoplakia, moniliasis and secondary syphilis. Patients may have lichen planus only in the mouth (figure 7), but similar involvement may be seen on the tongue and genitalia; in the latter area the lesions may be annular.

Figure 8 illustrates very well the flat-topped lesions and the silvery, glistening surface I emphasized. On involution of lichen planus, pigmentation occurs. Frequently, patients will come to you and say, "I still have lichen planus," because they misinterpret the significance of the pigmentation.

Lichen planus may be due to drugs or stress. Those of you who were in the service in New Guinea probably saw a number of men who developed the so-called New Guinea type of lichen planus after receiving Atabrine. It is important, therefore, to determine whether a patient has received Atabrine or some other drug known to cause lesions of lichen planus.

Treatment—Effects of therapy are good in

TABLE 4

DIFFERENTIAL DIAGNOSIS OF PAPULOSQUAMOUS SKIN DISEASES

DISEASE	ORAL LESION	LOCATION OF LESIONS	SEASONAL FLARES	LABORATORY STUDIES	EFFECT OF THERAPY
Psoriasis	No	Extensor surfaces	Yes	Biopsy	Fair
Pityriasis rosea	No	Torso	Yes	No	Good
Tinea versicolor	No	Torso	No	Potassium hydroxide	Good
Lichen planus	Yes	Flexor surfaces	No	Biopsy	Good
Discoid lupus erythematosus	Yes	Face and hands	Yes	Biopsy	Fair
Seborrhea	No	Scalp, face and shoulder girdle	Yes	No	Fair
Secondary syphilis	Yes	Generalized	No	Serologic test	Good

lichen planus, and x-ray treatment is of great help (table 3). It has greater application here than in psoriasis, because psoriasis is recurrent and lichen planus is not. Mercury, ¼ gr. two or three times a day, helps many patients. Bismuth may be given, either orally or by injection. Fowler's solution, 3 to 5 drops three times a day, often is beneficial in relieving pruritus. Using 3 to 4 tbs. of equal parts of WRIGHT'S LIQUOR CARBONIS DETERGENS® and Nivea skin oil in the bath water also often alleviates itching. Topically applied antipruritic remedies of various types, such as calamine lotion or liniment to which 1 per cent phenol or 0.25 per cent menthol has been added, may provide comfort. Sedation with phenobarbital or SERPASIL® is in order.

The third patient here today has lichen planus. His disease does not have the usual distribution, however, and this finding would make one think of psoriasis. The genitalia are involved. This patient has experienced stressful situations—death in his family and unpleasant employment—and these are factors which may be very important in the etiology and severity of his lichen planus. He is receiving ultraviolet light and bismuth in the form of BISTRIMATE® by mouth.

Pityriasis Rosea

Pityriasis rosea is a skin disorder which tends to occur in the spring and fall. Oral lesions are not seen. It usually involves the torso, and may be seen rarely on the neck or face. Laboratory studies are not of great help in establishing the diagnosis. Therapy is effective, usually requiring about six weeks for clearing.

Tinea Versicolor

Tinea versicolor, a ringworm infection of the skin, belongs in this group of papulosquamous diseases. Oral lesions do not occur, and it tends to involve the torso. There are no seasonal variations, although the condition may appear different at various times. The laboratory finding of importance is the potassium hydroxide examination which will reveal the characteristic mycelia. Therapy will clear the disease.

Seborrhea

Seborrhea never involves the oral cavity. It occurs on the scalp, face, chest and back and tends to be seasonal. Many patients with seborrhea note that they are better in summer than in winter. Therapy should be aimed at controlling the disease with a drug such as SELSUN®, for the scalp.

Secondary Syphilis

Secondary syphilis may mimic any of the papulosquamous skin diseases, and for that reason one should do a serologic test for syphilis whenever in doubt.

I have outlined in table 4 the general characteristics of the conditions discussed herein, as an aid in differential diagnosis.

The Treatment of Bulbar Poliomyelitis

MARTIN H. SEIFERT*

Northwestern University Medical School, Chicago

MARTIN H. SEIFERT

In any epidemic of poliomyelitis, the death rate occurs largely in cases of the bulbar type. A large percentage of this mortality is furnished by patients with paralysis of respiration and deglutition. The immediate cause of death may be the severe infection and paralysis, but, in my opinion, many deaths are due to drowning. The throat and bronchial tubes fill with a profuse secretion of mucus which the patient can neither swallow nor raise."

This quotation is from a paper on "The use of postural drainage in the treatment of bulbar poliomyelitis," by Dr. Jay I. Durand of Seattle, published in the J.A.M.A. of October 5, 1929, in which he described the spectacular results of postural drainage in two moribund patients with bulbar poliomyelitis.

Wilson in 1932 suggested that tracheostomy occasionally might be useful in this disease. However, neither his suggestion nor Durand's attracted any following.

When Galloway and I reported a series of cases at the American Medical Association meeting in 1949, Albert G. Bower of Los Angeles County showed us the chart of a patient on whom he had done a tracheostomy with recovery in 1933. He had not associated the procedure with the recovery and had not performed tracheostomy in any other such case until 1943, when Galloway reported his first cases.

In August 1943 a large 35 year old man was admitted to the communicable disease service at Evanston Hospital and rapidly progressed from restlessness to disorientation and then to coma in the course of a fulminating bulbar poliomyelitis. An alert supervisory nurse suggested to the resident and interns struggling to maintain the man's life that she thought the victim was choking. She called Dr. Galloway from the floor below, and he

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Presented before the fortieth annual Assembly of the Interstate Postgraduate Medical Association at Milwaukee.

found the patient comatose, cyanotic and almost pulseless. Laryngoscopy revealed viscid secretions and vomitus covering the larynx. Slight improvement followed suctioning, but the rapidity with which mucus and saliva accumulated astonished him and rendered his efforts fruitless.

Dr. Galloway suggested that the situation was not greatly different from that present in laryngotracheitis and that tracheostomy to clear the airway might save the man's life. Tracheostomy was done immediately, during which the patient became pulseless and ceased breathing. He was placed in a respirator, postural drainage was instituted, the bronchial tree was irrigated and aspirated, and a suction catheter was placed in the nasopharynx. In 30 minutes his pulse and color were good, and in 45 minutes the patient was conscious and rational and anxious to get out of the respirator. He is living and well 12 years later.

If this patient had died, his death would have been ascribed to an overwhelming infection in the brain stem with destruction of cardiovascular and respiratory centers. It appears obvious that the treatment administered did not influence the course of such an infection; the only factor it corrected was the secretional respiratory obstruction and its attendant anoxic state.

Galloway reasoned that this type of death in bulbar poliomyelitis, which I had witnessed many times, was entirely comparable to drowning and probably could be prevented by adequate and timely intervention. We have followed this line of reasoning since 1943 and feel that the attendant mortality of about 15 per cent is much better than the commonly accepted mortality of 35 to 50 per cent associated with previous treatment of bulbar poliomyelitis.

This incident covers all but the details of treatment as we now consider it. Our plea is for the maintenance of an open airway in the treatment of bulbar poliomyelitis.

The 1946 poliomyelitis epidemic in the Minneapolis area gave an excellent opportunity for large-scale trial of the method, and Priest, Boies and Goltz presented a favorable report on this experience in the June 1947 issue of the *Annals of Otology, Rhinology and Laryngology*.

The best treatment of bulbar poliomyelitis is still wholesome neglect and careful observation, but unfortunately only the patients with mild cases will survive under this regimen.

Remember that treatment begins the moment one suspects bulbar poliomyelitis, and this certainly should be evident when clearing of the throat, nasal regurgitation of liquids, and a palatal twang in the speech are apparent.

Dr. Montgomery was good enough to look up a very excellent case for me, and I think the patient demonstrates many things very well. (To the patient): You had a virus infection about the middle of August, is that right?

PATIENT: Yes.

DR. SEIFERT: And later on you had some trouble swallowing, and talking?

PATIENT: Uh-huh.

DR. SEIFERT: On August 29, I believe, you were sent to Southfield Hospital. What happened that morning?

PATIENT: I had to vomit, and after a while I couldn't get any air, so the doctor lifted my legs up in the air. (Spoken with a distinct palatal twang.)

DR. SEIFERT: He could not get rid of the vomitus, so they had to lift his feet in the air and hang his head over the side of the bed, and finally somebody slapped him on the back and knocked it out. You cannot keep doing that, however, because there may not be anyone with him when it happens, and then he would not be in his present condition.

Now I want to demonstrate his nasal twang. Say "wonderful."

PATIENT: Wonderful. (Nasal twang.)

DR. SEIFERT: Say "five and a half."

PATIENT: Five and a half.

DR. SEIFERT: "Istanbul."

PATIENT: Istanbul.

DR. SEIFERT: He had nasal regurgitation of fluid and talks like a person with a cleft palate. That is all you need. You take a tongue blade and a flashlight and look in the throat. If he does not have a cleft palate, he has bulbar poliomyelitis. We still see patients who have been talking like that for three days and some-

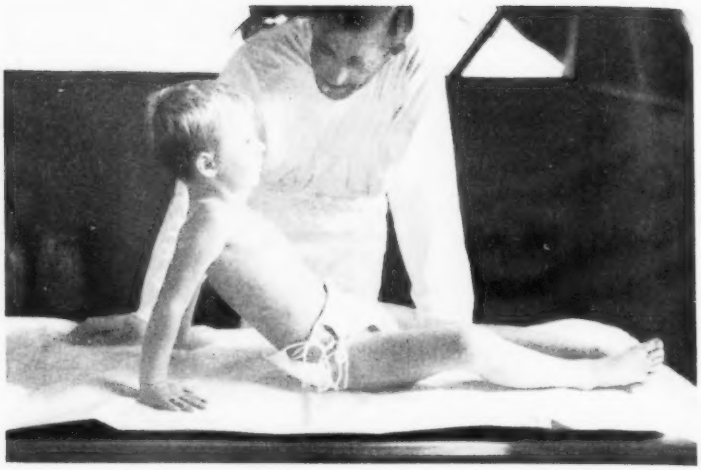

FIGURE 1. Characteristic posture of patient with poliomyelitis when asked to sit up.

body says they have a sore throat. Was your throat very sore?

PATIENT: No.

DR. SEIFERT: How did they feed you at first down at Southfield?

PATIENT: Intravenously.

DR. SEIFERT: Later on you went over to the County Hospital, and you were fed intravenously, I believe, from August 29 until October 4.

PATIENT: No, September 13.

DR. SEIFERT: Wait a minute here; I have to check this. I think we will show him how he was fed. You don't mind my putting this down your throat, do you?

PATIENT: Oh, oh, oh!

DR. SEIFERT: You wouldn't like this. This is the way he was fed after the first four or five days. A plastic 2 mm. tube was put through his nose into the stomach. It can be fastened on the side of the face and food can be put in through a syringe or a funnel, or it can be attached to an intravenous drip outfit.

He was fed a high protein, high caloric formula, starting out, perhaps, with 30 cc. every couple of hours, followed by a little water to wash out the tube. If the patient takes three feedings well that way, one can increase the amount to 60 cc.; if he takes three of these well, 90—120, maybe 150 cc. every two hours in a day or two. The intravenous feeding is cut down as the tube feeding is increased.

Usually if bulbar poliomyelitis is present there is also something else. This lad also had some weakness of one side of his face, which I will ask him to demonstrate: Pucker your lips to whistle; show your teeth; pinch your eyes shut tightly, now open wide; stick out your tongue; bite.

He still has some weakness of the anterior neck muscles, which I think are the most common single group of muscles involved in poliomyelitis. He also had some muscular weakness which I won't try to show you, but he is perfectly all right and back to normal, I think.

I want to thank this patient very much for coming, because I think the demonstration of the voice of a bulbar poliomyelitis patient is a priceless lesson.

Figure 1 illustrates the characteristic posture of a patient with poliomyelitis when one asks him to sit up.

As I said, treatment starts immediately. Table 1 summarizes the therapeutic measures. Transport the patient flat or on his abdomen with his head down if he is vomiting or having a great deal of trouble with secretions. Place him in a polio bed and use postural drainage.

A polio bed is a bed with a board under the mattress and a board at the foot end separated from the mattress by 4 in. wooden blocks so arranged that the foot of the bed can be ele-

TABLE 1

TREATMENT OF BULBAR POLIOMYELITIS

1. Transport patient flat, or on abdomen with head down.
2. Postural drainage in polio bed. Prone, or 15 degree elevation.
3. Continuous suction.
   Water suction (Venturi type).
   Central vacuum tank.
   Intermittent mechanical (stand-by).
   Catheter with two or three openings (near end).
   Connecting tube (2 mm. lumen).
   Breaker bottle.
4. Oxygen (catheter).
   With alcohol, trypsin or detergent.
5. Nutrition, fluids and electrolytes.
   a. *Intravenous* (cut-down if needed).
      Fluids and electrolytes (sodium and potassium).
      Proteins—plasma hydrolysates.
      Glucose, fructose, vitamin C.
      No vitamin B in acute stage.
   b. Gavage feedings (in three or four days).
      Plastic tube in stomach.
      Begin cautiously, increase as tolerated; high protein, high caloric formula.
   c. Cautious feeding by mouth.
      Beware of potatoes!
      Beware of sticky foods!
6. Tracheostomy *(high)* if indicated.
   Oxygen if needed.
   Humidification to prevent crusting.
   Irrigation and aspiration (3 per cent sodium bicarbonate and sodium chloride).
   Bronchoscopy through tracheostomy wound.
7. Respirator if needed.
   Collar depressed so that *tracheostomy tube is outside.*
   Support circulation with Levophed if needed.
8. Antibiotics *if needed.*
   Penicillin with streptomycin.
   Broad-spectrum agents (do not continue too long).
   Avoid sulfonamides in acute stage.
   No opiates or sedatives.
9. Careful watching at all times!
   Nurse constantly near.
   House staff on floor *at all times!*
   Keep up morale of patient.
   Personnel must exude confidence, based on adequate training.

vated. Placing a bed up on a chair does not provide postural drainage. Actually the angle required is about 15 degrees, and one just cannot get that angle by setting the foot of the bed on a chair; one needs a wooden horse of some kind or a jack. In recent years we have used a truck jack, which works very well—a tripod truck jack, and put them up high. I so often come into a room where the patient is in a respirator and is up about 5 degrees and somebody thinks it is 15. Actually, the top of the jack on a Drinker or an Emerson respirator is 15 degrees.

Let the head hang down a little if the patient is in a respirator so the hypopharynx drains out into the nasopharynx where there is suction.

Continuous suction is the only suitable kind. With intermittent suction, one is continually going in and out, and a No. 12 or 14 French catheter with a counter opening within ½ in. of the end will do a much better job if it is left in place with constant suction attached and will be much less traumatizing. Intermittent mechanical suction is a stand-by measure, but not for constant use.

The connecting tube must have a 2 mm. or larger lumen. We check all our connecting tubes when they are brought in, and anything with less than a 2 mm. diameter is discarded. I like a breaker bottle between the suction apparatus and the catheter so that if one is using water suction the patient won't be drowned by reversing.

Administer oxygen if necessary, but usually if oxygen is needed what one really needs is tracheostomy or bronchoscopy or both, or a cleared airway to be rinsed out with 3 per cent soda and saline.

Give fluids intravenously. Never allow a patient who has had trouble swallowing or who is vomiting to take anything by mouth. Regardless of whether you put fluids down by tube or whether he tries to swallow them, maybe the next time he tries he will choke and have his first "blue spell"; that will cut his chances of recovery about in half.

I think the patient should be given some proteins. I like plasma. The plasma hydrolysates perhaps do not contain enough protein, but they are of some help. Usually, intravenous feeding is necessary only for about four or five days, by which time vomiting has ceased. In fact, it usually ceases after the first day; maybe you notice a little motion returning in the back of the throat, in the palate,

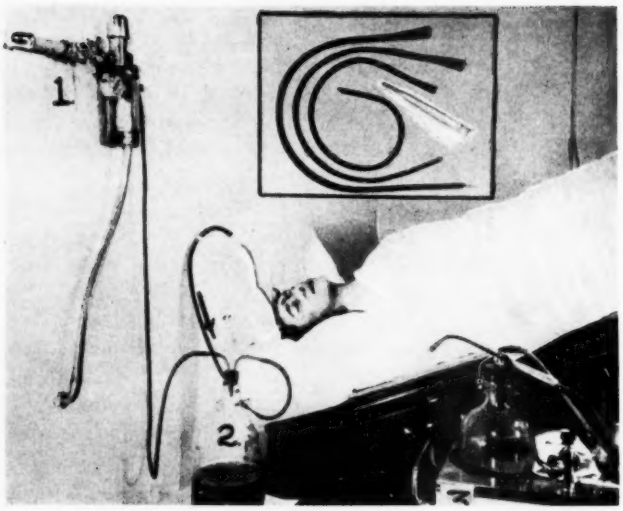

FIGURE 2. (1) Water suction fixed to the wall, connected by fairly stiff tube to collecting bottle. (2) This to catheter through patient's nose to the pharynx. (3) Stand-by mechanical suction. Beveled and whistle-tip catheters are shown in insert.

(Reproduced from *Laryngoscope*, June 1951.)

and this is the chance to put down this tube and start a good high protein feeding.

Give glucose, of course, or fructose, and vitamin C. I believe we have pretty good evidence that vitamin B should not be used. Dr. Fox was telling me that studies have shown that vitamin B is necessary to the growth of the poliomyelitis virus; we are not trying to grow poliomyelitis virus as a culture in our patients, so let's not give vitamin B. If one starves an animal of vitamin B, one will have a very hard time giving him poliomyelitis, whereas if one fills him full of vitamin B he will get it very easily. I would rather not use vitamin B during the acute stage of the disease.

With a plastic tube in the stomach, we give high caloric feedings. When I see motion returning, I like to try a little grape juice, which is purple and shows up well on tracheostomy dressings—and if it comes out of the tracheostoma the patient was not ready to swallow it, was he?

Beware of potatoes and sticky foods when cautious feeding by mouth has begun.

If simple postural drainage proves ineffective, then I want a tracheostomy, and I want the tracheostomy high, in the second ring.

If you use one of the trypsins, you *must*, as Dr. Fox frequently emphasizes, be sure there is constant suction in the throat with the patient in a position of postural drainage.

Maintain humidity in the room, or at least local humidity at the tracheostomy site to prevent crusting.

Irrigate and aspirate frequently, and by that I mean every 5 or 10 minutes at first, then every 15 or 20 minutes, then every half-hour and then every hour. Irrigate with the patient flat; aspirate with the patient in postural drainage position if necessary.

Watch for the first sign of atelectasis. Remember, not all patients with bulbar poliomyelitis are in a respirator. The patient here today was never in a respirator, although he was deathly sick. After all, it is usually spinal involvement that causes the respiratory paralysis, but remember that with bulbar poliomyelitis there frequently is upper spinal involvement. If you have a patient who turns from side to side and every time you turn him on his right side he goes black, that patient has an atelectasis. If a Bennett flowmeter or an Emerson gauge is available to measure the amount of air that comes out of the tracheostomy, or out of the mouth if the patient's neck is intact, I advise you to measure it. If his tidal air drops sharply, put a bronchoscope down. Doing so will not harm the patient, particularly through a tracheostomy.

Remember that the collar of the respirator

is depressed so that the tracheostomy tube is outside.

I have not found any drug which will support circulation as well as LEVOPHED®.

Antibiotics are given if needed. I like penicillin with streptomycin, and if you use a broad-spectrum drug please give it only if needed for complications, and not longer than four or five days. I do not believe in using antibiotics routinely. They are of no use in poliomyelitis; they are only useful for the secondary infections.

Make sure the patient is watched carefully at all times, with a nurse in constant attendance and house staff constantly on the floor. And keep up the morale of the patient.

Figure 2 shows the 2 mm. plastic tube in place, the catheter with one or two counter openings within ½ in. of the end. We now have a regular operating room-type suction. We formerly used this Venturi-type pump, and in the illustration you can see a stand-by unit for emergency use.

The LIPIODOL® bronchograms in figure 3 demonstrate why the 15 degree elevation of

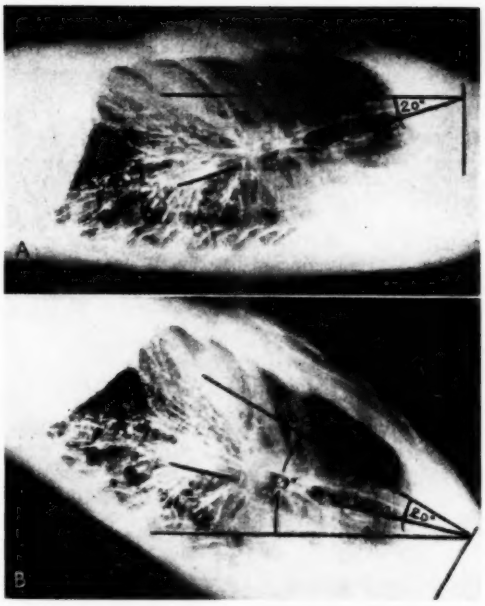

FIGURE 3. The lower airway is outlined with radiopaque oil. A. Declivity of trachea and bronchi from body axis. B. Minimum elevation necessary for useful postural drainage.

TABLE 2

INDICATIONS FOR TRACHEOSTOMY

DO TRACHEOSTOMY (HIGH) AT ONCE, IF

1. Patient comes in spitting constantly.
2. Airway cannot be kept clear of secretions.
3. Restlessness, disorientation or stupor develops (bulbar *or* spinal case).
4. Bulbar symptoms are rapidly progressive.
5. Laryngospasm or cord paralysis develops.
6. Blood pressure rises sharply, or cyanotic flush appears.
7. Signs of vasomotor failure develop.
8. Signs of respiratory failure appear. *(No bulbar polio patient in respirator without tracheostomy.)*
9. Untrained attendants, lack of cooperation of patient leave doubt that airway can be kept clear.

SINGLE INDICATION: *Any patient who requires postural drainage and suction more than a few hours needs tracheostomy.*

TABLE 3

POLIO DIET 1, FOR TUBE FEEDINGS

Principle: To provide the essential food nutrients in easily digestible form for acute cases of bulbar poliomyelitis and those requiring tracheostomy.

#1 St. Mary's Formula (Plain):
2000 cc. milk
400 cc. cream
200 cc. KARO®
100 cc. orange juice
6 eggs

Approximate food value per hundred cubic centimeters: 4 gm. protein, 6.7 gm. fat, 6.4 gm. carbohydrate, 112 calories (1,120 calories per quart).

#2 St. Mary's Formula:
#1 St. Mary's Formula, plus
100 cc. LIPOMUL® (10 per cent dextrose, 40 per cent vegetable oil)
120 gm. Protenum (42 per cent protein, 46 per cent carbohydrate, 2 per cent fat)

Approximate food value per hundred cubic centimeters: 9.04 gm. protein, 10.94 gm. fat, 12.92 gm. carbohydrate, 196.4 calories (1,964 calories per quart).

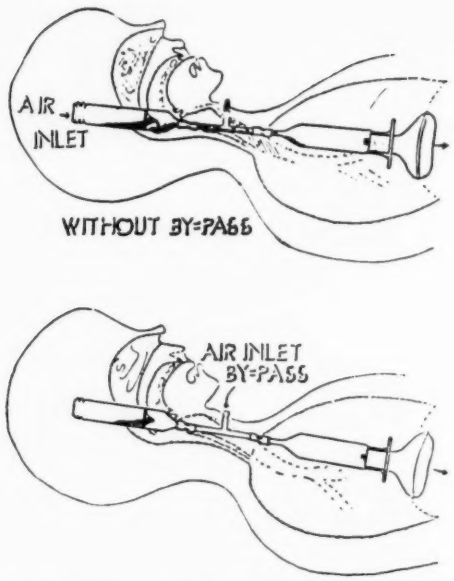

FIGURE 4. A model to simulate the effect of voluntary breathing or a respirator when there is fluid in the upper airway. With moderately viscid fluid, intravenous tube, T tube and ASEPTO® syringe, it acts as shown. When the by-pass is open, no fluid is drawn—illustrating the effect of tracheotomy.

(Reproduced from *Archives of Otolaryngology*, August 1947.)

FIGURE 5. Effect of tracheostomy on anatomic dead-space volume.

(From Affeldt, J. E.: Mechanical treatment of pulmonary failure. Postgrad. Med. 19:550-558 [June] 1956.)

the feet I talked about is necessary. The posterior declivity of the bronchi is 17 degrees.

Indications for Tracheostomy

I have never seen a patient who left the hospital alive if he came in spitting constantly and did not have a tracheostomy. Table 2 summarizes the indications for tracheostomy. Restlessness, disorientation and stupor usually do not mean encephalitis. I recall one case in which the patient developed what everybody thought was encephalitis three days after his elevated temperature returned to normal. We measured his tidal air and it was only 200 cc. What does that mean? Of that 200 cc., 150 cc. was dead space; 50 cc. was alveolar exchange. All we did was a tracheostomy. He had been irrational for two days, and 10 minutes after the tracheostomy he was perfectly rational. His air exchange was not any greater, but he now had only 50 cc. of dead space. If one cannot provide an open airway immediately and keep it open with constant suction and postural drainage, tracheostomy should be done.

Figure 4 shows what tracheostomy does. You can see that inspiration will not suck that thick mucus down through the larynx and into the lung.

Figure 5 demonstrates the dead space principle. Dr. John E. Affeldt of Los Angeles was kind enough to leave this slide; he showed it also with his presentation.

The diets we use for tube feedings are varied according to the patients' needs (table 3). Formulas of skim milk, MERITENE® and PROTENUM® as shown in table 4 provide variable protein and fat mixtures. We also use SUSTAGEN® formulas (table 5). One can give a very high caloric content and high protein content, as desired and tolerated.

When the patient is able to swallow a little, polio diet 2 is given (table 6). It consists of strained citrus juices, apple juice, clear broths,

TABLE 4

TUBE FEEDING FORMULAS FOR PATIENTS WITH BULBAR POLIOMYELITIS*

Skim milk formula:
120 gm. dried skim milk powder
720 cc. skim milk
50 gm. sugar
4 eggs

Approximately 1000 cc.; 120 calories per hundred cubic centimeters, 9.3 gm. protein, 2.6 gm. fat, 15 gm. carbohydrate.

Meritene formula:
175 gm. Meritene
860 gm. skim milk

Approximately 1000 cc.; 91 calories per hundred cubic centimeters, 8.6 gm. protein, 0.1 gm. fat, 13.7 gm. carbohydrate.

Protenum formula:
240 gm. Protenum
860 gm. skim milk
1 tbs. sugar

Approximately 1000 cc.; 150 calories per hundred cubic centimeters, 12.7 gm. protein, 0.5 gm. fat, 16.1 gm. carbohydrate.

*The variety of formulas listed for tube feeding gives a selection of foods with varying concentration both as to caloric content and as to the balance of carbohydrate, protein and fat desired for the individual patient. It also makes some allowance for sensitivities on the part of the patient. Usually, after the acute viral infection has subsided, a multiple-vitamin preparation is added to the formula.

TABLE 5

SUSTAGEN FORMULAS

1. 900 gm. Sustagen
   1500 cc. water
   2100 cc.; 3500 calories; 210 gm. protein, 30 gm. fat, 600 gm. carbohydrate.
2. 750 gm. Sustagen
   1250 cc. water
   1700 cc.; 2900 calories; 175 gm. protein, 25 gm. fat, 500 gm. carbohydrate.
3. 600 gm. Sustagen
   1000 cc. water
   1400 cc.; 2300 calories; 140 gm. protein, 20 gm. fat, 400 gm. carbohydrate.
4. 300 gm. Sustagen
   500 cc. water
   700 cc.; 1100 calories; 70 gm. protein, 10 gm. fat, 200 gm. carbohydrate.

TABLE 6

POLIO DIET 2

A few cubic centimeters of grape juice are given first to determine the patient's swallowing reflexes.

Grape juice usually is well tolerated and its color is readily discernible. If the patient is incapable of swallowing, the juice returns through the nose or appears in the tracheostomy suction.

Other foods in addition to the Polio Diet 1 are:

Strained citrus juices—diluted
Apple juice
Clear broths
Tea with sugar
Jell-o

Milk and cream apparently produce more mucus, hence are undesirable at this stage.

tea with sugar, JELL-O® and grape juice.

Diet 3 adds some soft foods (table 7). We are still in the process of building these diets, trying to get information from patients about what they swallow most easily.

Polio diet 4 allows a good many foods (table 8). Potatoes and sticky cheese dishes are among the most deadly.

I would ask you, then, to consider these 10 commandments in treatment of bulbar poliomyelitis.

1. Do not give opiates or sedatives to these patients. Restlessness equals anoxia.

2. Do not allow food by mouth if there is vomiting or more than the slightest swallowing difficulty.

3. Keep patients prone or in postural drainage position with the head down, and provide constant nasal suction if there is any accumulation of secretions in the pharynx.

4. If the aforementioned measures do not immediately clear the pharynx and keep it clear, do a tracheostomy.

5. Do not save tracheostomy for use as a last-ditch procedure. You may win occasionally, but not often.

6. Never put a bulbar poliomyelitis patient in a respirator without a tracheostomy.

7. Any supportive measure to keep a patient with bulbar poliomyelitis alive through the acute stage is worthwhile. I had one patient who was a complete vegetable for more

TABLE 7

POLIO DIET 3

Principle: To supply a diet of soft, easily digested foods, low in fiber, to be used for a short period as the patient learns to swallow more effectively.

FOODS ALLOWED: All foods listed in Polio Diets 1 and 2, plus:

- Soups—Bouillon, strained meat soup
- Cereals—FARINA® or CREAM OF WHEAT® with lots of sugar and very little milk (sugar cuts mucus)
- Eggs—Poached; soft-boiled
- Fats—Butter as desired
- Vegetables—Well cooked and puréed
- Fruits—Puréed, cooked or canned fruits (without seeds, coarse skin or heavy fiber); strained fruit juices
- Desserts—Sherbet, Jell-o
- Meats—Well cooked and puréed
- Beverages—Tea with sugar; water

FOODS TO AVOID:

- Strong-flavored vegetables (cabbage, cauliflower, onions, turnips)
- Foods with seeds (berries, tomatoes)
- Fried foods
- Raw fruits and vegetables
- Rich pastries
- Highly seasoned and spiced foods
- Potatoes
- Starchy products (macaroni, spaghetti, rice, etc.)
- Sticky foods (cheese dishes, oatmeal, ice cream)
- Milk
- Fish
- Coffee

TABLE 8

POLIO DIET 4

Tube feedings are gradually eliminated as patient's ability to swallow improves.

FOODS ALLOWED: All foods from Polio Diets 1, 2 and 3, plus:

- Ground beef, lamb, chicken or turkey, with light gravy or mayonnaise
- Soda crackers, white bread or toast, with butter
- Simple cornstarch puddings; ice cream
- Well-cooked vegetables (not puréed), such as carrots, canned peas, French-cut green beans, asparagus tips, squash, chopped spinach
- Cooked or canned peaches, pears, apricots, applesauce
- Milk
- Milk, with protein supplements such as Protenum, Meritene, skim milk powder, Sustagen
- Carbonated beverages (in moderation)

FOODS TO AVOID:

- Potatoes, noodles, macaroni, cheese dishes and casseroles having a sticky consistency (no potatoes until very sure of patient's ability to swallow well)

Note: Patients having spinal poliomyelitis are able to tolerate a soft to full general diet, depending on the individual patient. This diet includes potatoes, starches, milk and boned fish. All patients are placed on a *high protein diet* as they become able to handle a full diet.

than two weeks, with circulation supported only by Levophed; she now rides a bicycle and plays like any other child.

8. Remember that in an emergency your anesthesiologist may help by intubating the larynx, but then do the tracheostomy as soon as possible.

9. Constant watchfulness and attention to detail are necessary, and nursing care is paramount in importance. The house staff should be available at all times to meet emergencies, and a nurse must be near the patient constantly.

10. Pediatrician or internist, neurologist, anesthesiologist, laryngologist, orthopedist, physiotherapist, house staff and nursing staff must constitute a team in the care of these patients, and the reward is great, for these are young people who have not yet had a chance to live.

Fracture-dislocations of the Thoracolumbar Spine With Spinal Cord Injury

E. HARRY BOTTERELL*

University of Toronto, Toronto

E. HARRY BOTTERELL

THE fate of patients with spinal cord injuries was revolutionized during World War II, first by improved evacuation and management of casualties and second by the advent of the antibiotics and the sulfonamide drugs. In World War I, in all the Allied armies, 90 per cent of all the men who sustained spinal cord injuries and had paraplegia died within six months. Of the 100 such patients we have followed since World War II, 75 per cent are still going strong. In 1954, not one was in the hospital. This new concept of spinal cord injuries, that such a patient may become a useful citizen, influences our approach to the problem.

Consider the results of the treatment of a series of patients with thoracolumbar injuries during the past 10 years at our hospital, that is, comminuted fractures of the neural arch and compression of the body of L1 or T12 or, more commonly, a fracture-dislocation at T12 or L1. Only 15 patients in that large group are in the hospital, and more than 50 per cent of those who are out of the hospital are gainfully employed.

This objective can be achieved by a team which includes a neurologist and perhaps a plastic surgeon, and a physician extraordinary who begins following the patient when he comes under neurosurgical care and continues throughout his rehabilitation.

The patient who is here today represents all that is good in the management of spinal cord injuries. He sustained a fracture-dislocation at T12-L1. He has only some power in the left quadriceps. His bladder and bowel are profoundly paralyzed, with lack of normal sensation. After 14 months of treatment for his spinal problems and rehabilitation, he is now at home. He works as a silversmith, looks after himself, independent of nursing and orderly care, and hopes to be employed as a skilled tradesman when he completes his training in that field of endeavor. It would be hard to find a finer example of the management of such a patient and of the patient's own suc-

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cess at rehabilitation—because it is the patient's success, not ours, by virtue of the huge effort he must make.

How do we promote this objective? A lateral roentgenographic view of a classic fracture-dislocation at T12-L1 shows clearly that the intervertebral disk is torn, the supraspinous ligament is ruptured, and the facets are either fractured or dislocated. What is the significance of this picture in terms of the patient's neurologic deficit?

The lower end of the spinal cord ends at about L1 and is surrounded by roots of the cauda equina. Fracture-dislocation at T12-L1, if it damages the spinal cord, is irreversible in most cases, in our experience, but the roots that supply the quadriceps, L2, L3 and L4, are much more resistant to injury. They come off above the level of the injury, and if one can achieve root preservation or root recovery the patient's life is infinitely more tolerable because he has flexion of the hips and contraction of the quadriceps—and that makes a huge difference in the life of a paraplegic.

The L1 and L2 roots come off a great deal higher sometimes, so there are two components to the neural injury at this level: (1) injury to the conus medullaris or the lower end of the cord supplying the bladder and bowel and (2) injury to roots which supply particularly the quadriceps and the flexors of the hip, the psoas muscles.

I recently gave a lecture before a group of 40 young medical officers in the armed forces, and I asked them, "How many of you have encountered the following situation: A patient has great pain in his back; you order him evacuated by stretcher-bearers, and when you see him in the hospital he not only has the pain in his back but is paralyzed?" Six hands went up. I myself have seen three patients with just such a history. The most tragic was a young woman who was in an automobile accident on her wedding trip. One of my colleagues saw her at the scene. She was moving her legs as she lay on the highway and was paralyzed on the x-ray table.

That raises the question of how to evacuate patients. I give a lecture to students every year on this subject, and they remember only one thing: "That is the lecture where Dr. Botterell made us lift the patients." Mr. Roy T. Ragatz, this Association's executive director, has volunteered to be the subject for this demonstration, and I will call for four men from the audience to help with the lifting.

There are different schools of thought as to how one should lift these patients. We teach that persons with pain in the back or neck, numb legs or paralyzed legs should all be lifted one way. I will ask one of our helpers to take hold of this man's ankles, and two men to slip their hands under him, and I will take the head. The patient's arms are not paralyzed, so he can hold them in place. Remember the x-ray in a case such as this—the vertebra riding forward, forceful flexion and a shearing effect, and maybe it just has not ruined those roots. The cauda equina clusters around the conus medullaris. One cannot do any harm by pulling straight. I put my right hand under his occiput and my left hand under his chin, and I say to my colleagues, who have their hands underneath, "Now lift and pull"; I am pulling quite hard. There is one blanket folded to fit the patient's lumbar curve, and a second blanket is under his shoulders, so there is slight backward extension of his head.

Having lifted this patient, what does one lift him onto? We use Stryker frames. They were pioneered in the United States, and last summer I heard high praise for them when I was in England. Casualties evacuated there from Korea arrived without pressure sores. When a patient is brought to the hospital who you suspect may have a fracture-dislocation or who has a spinal cord injury, we believe he should be lifted as I have demonstrated, from the stretcher onto the Stryker table.

These patients, in the acute phase, require the combined treatment available at a center for spinal care. Sometimes, at our hospital, we get patients from 400 miles away; times without number, we have seen patients who were put on their backs in a hospital, left on their backs in a hospital, and by the time they reached us two or three days later they had pressure sores over their heels and sacrum which take weeks to heal. A patient on a Stryker frame can be turned over every time

his skin becomes red. This principle of treatment has improved the long-distance evacuation of these patients. Simply rolling the patient over in bed has a shearing effect. Bear in mind that the spine is unstable, the disk is torn and the ligaments are torn, and if the nerve roots are not gone, they certainly will be gone after the patient has been rolled over a few times. Also, use of the Stryker frame saves thousands of nursing hours.

Preventing paraplegia is the most important part of the management of a spinal cord injury. These patients fall into the hands of the police force, first-aid men and ambulance drivers. The prevention of six paraplegias, spinal cord injuries, is more than any neurosurgeon will achieve almost in his whole life in dealing with trauma to the spinal cord.

The patient I presented earlier walks and works. He walks with long leg braces and crutches. He shifts himself from chair to bed and from chair to toilet very skillfully, as do the patients whom Dr. Jousse, my colleague, has helped to rehabilitate.

What is the surgeon's responsibility in cases of this type? Gallie taught me years ago that fractures of the spine are like fractures anywhere else; one must reduce them and fix them. At that time it did not seem very important, because such patients did not survive. Now, however, it is very important. First of all, a patient with an unstable lumbar spine and an incomplete lesion may lay down enough callus over 20 years to lead to quite a substantial increase in his paraplegia, and I have such a case. Second, a patient who is brace-walking with crutches (which not many of our patients do, because it is too difficult) or living a wheel chair life—shifting from chair to motor car and motor car to chair, going to work every day—has to have a comfortable back. So, led by Professor Gallie in about 1936, we set out to reduce these fractures, to reduce and fix them—first Professor Gallie and myself and more recently Dr. Dewar and myself at Toronto General Hospital.

At operation, we do a partial hemilaminectomy and inspect the extradural space, because in 10 per cent of these cases there is a herniated fragment of bone or disk in the spinal canal, and to reduce the dislocation would do further injury to the cord unless the fragment were removed first. We do not do "flat out" laminectomies. We inspect the intraspinal canal at the site of injury by virtue of a partial hemilaminectomy, and there is constant conflict because I do that part and the reduction, and Dr. Dewar does the fixation; he is forever after me not to take out so much bone. This is important, because we now have had experience with several patients who had widespread laminectomies and who had a greatly increased spinal deformity and dislocation as a result.

It is extremely difficult to assess the results of treatment. Of all the patients we have operated on over a five year period, not one who had complete paralysis of bladder and bowel with loss of the appropriate skin innervation and muscle innervation, has ever recovered bladder function. That, we believe, is because the conus medullaris is injured. What is important, however, is root preservation—to set the stage for recovery of root function—and that is done by reducing the dislocation, removing any intraspinal masses such as disks or bone fragments so that the roots can recover to the best advantage. Of course, the T12-L1 is the area of maximum injury just as it is the area of maximum dislocation.

This is a new era in terms of being able to allow paraplegic patients to rehabilitate themselves. It requires the combined efforts of a team, and in our center Dr. Albin Jousse has become the physician extraordinary to some 500 patients with spinal cord injuries. He starts with them the same day that the surgeon starts with them on the neurosurgical service, and then they are under his care when they have stable spines.

Knowing that this is a new era in paraplegia, it is incumbent on us as doctors to evacuate these patients to a spinal center at the earliest opportunity. This is achieved to the best advantage by lifting patients correctly and, we believe, by transporting them on Stryker frames. The great majority of patients with spinal cord injuries are capable of restoring themselves to useful life at home, independent of nursing care, and of working.

CLINICOPATHOLOGIC CONFERENCE

Report From Veterans Administration Hospital, Hines, Illinois

Case Report

THE chief complaints in this case were (1) cramping pains in both legs of four weeks' duration, (2) numbness and tingling of the left ankle of three weeks' duration, and (3) coldness of extremities of two weeks' duration.

A 30 year old Negro man suddenly experienced cramping pains in the calves of both legs while walking home following a long day of work as an elevator operator. The pain was severe enough to require him to rest. During the four weeks from this first attack to the patient's admission to the hospital, the leg pains were aggravated by walking and standing but relieved by rest. Occasionally he had pain in both calves while in bed; this pain was particularly severe. He had not worked since the onset of his illness.

Three weeks before admission, numbness and tingling of the left ankle developed. The patient said his ankle felt as if it had "gone to sleep." He called a physician, who prescribed bed rest and various pills.

Two weeks before admission the patient noted coldness in both lower extremities. At first this symptom involved only the feet, but the coldness progressed upward until at admission it affected both calves to the knees.

The patient stated that a week prior to his illness—that is, five weeks before admission—he had experienced night sweats associated with chills and fever, lasting about one week. Also, during his entire illness he had marked anorexia, but he did not give a history of cough or any cardiovascular disease.

Past history—The patient admitted to excessive use of alcohol and said he smoked one package of cigarettes a day. In 1944 while in the Army, he had syphilis and was treated with "arm shots" for six months. Following discharge he received an additional 10 day course of penicillin at a treatment center. At that time, a spinal fluid examination was reported to be negative. He also gave a history of drinking large amounts of water and urinating frequently, the latter a lifelong habit.

Physical examination—The patient was well developed and well nourished and appeared acutely ill. His temperature was 100.2° F. He moved slowly because of pain in the calf of his left leg. The thyroid gland was slightly palpable on swallowing. Examination of the eyes gave essentially normal findings. Funduscopic study revealed only physiologic cupping of the disk. The ears were essentially nor-

mal. There was moderate injection of the nasal mucosa with evidence of a mucopurulent discharge. The mucous membranes of the mouth and throat were not injected. An orange-yellow discoloration was noted in the middle portion of the tongue.

The chest was normal in size, shape and symmetry. The lungs were clear throughout, with no rales audible. Dullness was noted to percussion just above the left base posteriorly, where the examiner heard increased breath sounds and voice sounds but no friction rub.

Blood pressure was 146/110, and the pulse was 120. Cardiac enlargement was not evident. A soft systolic precordial murmur was heard, most pronounced at the apex.

Examination of the abdomen revealed voluntary rigidity throughout, although the patient was able to relax. The liver, spleen and kidneys could not be palpated. There was tenderness in the left hypochondrium. Abdominal masses were not felt.

Rectal examination was negative. There was no spinal tenderness, but mild tenderness was noted at the left costovertebral angle. Pitting edema of the ankles was absent. The dorsal skin of the left foot was mottled.

Peripheral pulses, including femoral, popliteal, dorsalis pedis and posterior tibial arteries, could not be palpated in the lower extremities. Homans' sign was positive on the left. The calf of the left leg was extremely tender. The right radial pulse was not palpable, although the brachial pulsations were felt on both sides. Pulsation of the left radial artery was somewhat diminished. Both lower extremities were cold, from the inguinal regions downward. Clubbing of the fingers and curving of the nails were noted, and the patient said these had been present as long as he could remember.

Neurologic examination disclosed hyperactive reflexes in the upper and lower extremities. Babinski's, Oppenheim's and Chaddock's signs were negative. Hoffmann's sign was positive bilaterally. Anesthesia to pinprick of the left foot extended to the ankle. The remainder of the neurologic examination was negative.

Laboratory data—Table 1 summarizes the laboratory findings.

TABLE 1

LABORATORY FINDINGS

11/4	Urinalysis: acid, specific gravity 1.032, albumin 3 plus, sugar negative; 60 white blood cells per high power field, 6 red blood cells.
11/5	Bleeding time, 1 minute 10 seconds. Coagulation time, 2½ minutes. Prothrombin time 13 seconds, 100 per cent. Sedimentation rate, 20 mm.
11/6	Glucose 147, protein 7.6 gm. (3.6:4.1), cholesterol 145. Carbon dioxide-combining power 58 per cent.
11/9	Urinalysis: acid, specific gravity 1.025, albumin 2 plus, sugar negative; 60 white blood cells per high power field, occasional red blood cell, occasional granular casts (centrifuged specimen). Hematocrit 40; red blood cells 4,650,000; white blood cells 20,400, polymorphonuclear leukocytes 68, lymphocytes 22; hemoglobin 14 gm.; coagulation time 2 minutes 30 seconds (11:30 A.M.), 3 minutes (5:30 P.M.).
X-rays	
11/5	Chest: no lung pathology. Prominent left ventricle. Transverse diameter of heart 14.5 cm. (chest 28.4 cm.). Pelvis normal. No calcification of blood vessels in lower extremities; bones normal.
11/9	Portable chest x-ray: heart markedly enlarged, lung fields essentially clear.
Electrocardiograms	
11/5	Sinus tachycardia. Transient coronary insufficiency.
11/9	Abnormal; coronary insufficiency.

Hospital course—The patient was admitted to the medical service. Therapy consisted of codeine for relief of pain, papaverine, 3 gr. four times a day, and sedatives. He was extremely uncomfortable and complained of leg pain. On November 5, the day after admission, 5 cc. of tetraethylammonium chloride was given intramuscularly, and this provided some relief. He was seen on the peripherovascular service and transferred to that ward the following day, November 6. A bilateral lumbar block was then accomplished, with some slight increase in temperature in both legs. The patient stated that for an hour and a half following this procedure he obtained some relief of pain.

FIGURE 1. Line of demarcation of dry gangrene of left foot.

On November 7 the left foot and leg were appreciably darker and gangrene appeared almost certain (figure 1). On November 8 a continuous sympathetic block was started—5 cc. of 0.5 per cent procaine every hour.

On November 9 his temperature had risen to 101° F. The ward surgeon detected a gallop rhythm. A cardiologist saw the patient and confirmed the finding of a gallop rhythm but did not detect any murmurs. His impression was early left ventricular failure. The patient was started on digitalis, oxygen therapy and intravenous heparin (50 mg. every six hours). At 7:30 that evening he went into profound shock. His heart rate became too rapid to count, the gallop rhythm persisting. In spite of the use of intravenous fluids and blood transfusions, the patient died at 8:05 P.M.

Discussion by Medical Consultant

DR. DAVID I. ABRAMSON: This case suggests a number of possibilities as to the cause of illness. Obviously at least a part of the clinical picture is explainable on the basis of a widespread occlusive vascular disease acting very rapidly to occlude the main vessels in the lower extremities and at least one of the smaller arteries in the upper extremities.

Essential polyarteritis comes to mind first. (This perhaps is a better term than periarteritis nodosa, since all the layers of the vessels are involved and in most cases nodules are not present.) In favor of this entity are the following: (1) The illness began with findings of a generalized infection. Then signs of occlusion of the peripheral arteries appeared, eventually leading to impending gangrene; (2) there were signs of kidney involvement—both urine specimens showing the presence of albumin, white blood cells in large numbers, red blood cells (a considerable number in the first specimen and fewer in the second) and occasional granular casts in the second.

It would have been of interest to have the results of kidney function tests—phenolsulfonphthalein, nonprotein nitrogen, concentration and urinary sediment. Some workers, particularly Krupp, have shown that examination of urinary sediment provides a means of differentiating the various stages of glomerulo-

nephritis and visceral angiitis-polyarteritis and lupus erythematosus disseminatus. In the initial stage of glomerulonephritis the urine contains numerous red blood cells and red blood cell casts, whereas the second stage, in which there is tubular degeneration, is characterized by the presence of fat in the urine, as droplets in hyaline casts and in the epithelial cells of the tubules. Red blood cells are present, but not in the form of red blood cell casts. There are large amounts of protein in the urine, and blood protein is reduced. In the terminal or third stage the flow of urine is so slow in some of the collecting tubules that large casts, known as broad cells or renal failure casts, are formed. In this stage, hypertension and retention of urea are quite marked. It is very rare to find the characteristics of the three stages in the same urine specimen in a case of glomerulonephritis, but in visceral angiitis this does occur. For example, in polyarteritis one may find in the same specimen red blood cells and red blood cell casts (first stage), oval fat bodies and fatty and waxy casts (second stage) and, frequently, renal failure casts (third stage), as well as large quantities of protein.

It is possible that in this case the kidney findings existed before the onset of the acute illness and were due to a nephritis, related to the scarlet fever the patient had in childhood. Examination of the urinary sediment would have helped to clarify this point.

Further findings in favor of polyarteritis are the tachycardia, leukocytosis, atypical electrocardiographic changes, vague abdominal symptoms, nonlocalizing neurologic abnormalities (hyperactive reflexes and positive bilateral Hoffmann's sign), and, finally, the rapid progress of the disease, terminating in the patient's death.

Against the diagnosis of polyarteritis are the absence of a history of allergy or intake of such drugs as the sulfonamide compounds, absence of muscle pains and arthritic manifestations, and a normal red blood cell count and hemoglobin in the absence of eosinophilia. Eosinophilia is present in about 50 per cent of cases of polyarteritis; therefore it is not essential for the diagnosis.

Another entity which we must consider, one which also has widespread manifestations and involvement, is thromboangiitis obliterans (Buerger's disease). This condition affects the arteries of the upper as well as the lower extremities and eventually may progress to gangrene. Furthermore, the entity is not limited to the vessels of the limbs; the pathologic process has been reported in the cerebral vessels, the coronaries, the gastrointestinal tract and elsewhere. Associated with the occlusive process is a certain amount of vasospasm, due to involvement of neighboring mixed nerves (including the sympathetics) in the pathologic process—that is, in the perivascular reaction affecting the blood vessels. Evidently, vasospasm played an important role in this case, judging by the fact that tetraethylammonium chloride and paravertebral sympathetic block relieved the pain in the leg and foot. Tetraethylammonium chloride, by paralyzing the lower ganglia (parasympathetic as well as sympathetic), and procaine block, by paralyzing the paravertebral sympathetic ganglia, break the continuity of the nervous pathway over which the impulses arising in the vasomotor center reach peripheral blood vessels. In this case, relief was experienced as a result of an increase in blood flow to the peripheral tissues due to inhibition of the vasomotor tonus. Of course it is possible that this occurred as a result of removal of normal vasomotor control rather than of loss of an abnormal degree of vasospasm.

There are a number of points against the diagnosis of thromboangiitis obliterans. First, the patient was a Negro. The literature has only about eight or nine reports of Buerger's disease in Negroes. Generally the condition begins insidiously, the first symptom being intermittent claudication. There is no history in this case of any difficulty in walking prior to the onset of the acute episode. Even the initial symptoms were not those of typical intermittent claudication, since the cramp in the calves was probably present at rest, at times, and was aggravated by walking. Furthermore, it was present on standing. In true intermittent claudication the pain—the sense of tiredness, the fatigue, the cramp—is present only with

physical exertion which utilizes the muscles affected, and the symptoms disappear after termination of the exercise, even if the individual does not sit down. Symptoms of true intermittent claudication are never present when the patient is at rest.

Thromboangiitis obliterans rarely progresses as rapidly as occurred in this case, nor is it associated with systemic reactions. If we assume that the patient did not have symptoms prior to the acute episode, then the condition was of only six weeks' duration. Certainly the type of death is not at all typical of Buerger's disease.

The next possibility is occlusion of the aorta at its bifurcation. Leriche, in France, has described an entity of slow thrombosis of the aorta at this site in young men which is ushered in by difficulty in erection and in which signs of occlusive arterial vascular disease and even gangrene of the lower extremities subsequently appear. However, the existence of vascular occlusion in the upper extremity in this case, the kidney findings and the systemic reaction probably rule out this possibility.

Multiple embolic phenomena can also be considered, with lodgment of the emboli in the main vessels of the lower extremities and in the radial artery on the right side. Against this diagnosis are the absence of any heart disease conducive to the formation of thrombi and the absence of a sudden onset of pain, anesthesia and color changes in the involved extremities, part of the picture of an embolic affair. The symptoms were present for several weeks before impending gangrene appeared. If an embolus were to lodge in the femoral or iliac artery or at the bifurcation of the aorta, one would expect the onset of gangrene in several days, especially if treatment were not instituted. Furthermore, an embolus to the right radial artery should have produced some symptoms in the right hand; none were recorded in this case.

In view of the history of syphilis, we must consider the possibility of multiple aneurysms, particularly one involving the aorta near the bifurcation with subsequent thrombosis occluding the iliacs. However, syphilis is the cause of abdominal aneurysms in only 5 to 10 per cent of cases, and even in these instances arteriosclerosis is also present. There is nothing in the protocol to suggest that the patient had arteriosclerosis. It is also questionable whether the interval between the syphilitic infection and the present illness was great enough to permit the formation of aneurysms. Finally, this diagnosis would not explain the systemic reactions.

The final entity I would like to discuss is disseminated non-necrotizing arteritis, which is similar in many respects to lupus erythematosus disseminatus and polyarteritis but with more outstanding vascular manifestations. The clinical course, however, is the same in the three conditions. The cutaneous lesions of lupus and the endocardial lesions of Libman-Sacks' disease are not present in disseminated non-necrotizing arteritis, nor is there any eosinophilia either in the peripheral blood or around the arteries, or medial necrosis of the arteries, as is present in polyarteritis. Like these diseases, disseminated non-necrotizing arteritis is progressive and fatal. Large arteries may be occluded, as in this case, with gangrene of the digits and even local portions of the skin. Progressive fever and evidence of involvement of the spinal cord and brain and other organs may be seen. The findings in the present case fit this entity quite well.

Several points are not clear to me. The history of drinking large quantities of water and urinating frequently may indicate diabetes insipidus. There is nothing further to substantiate this diagnosis. The presence of an elevated blood sugar on one occasion is not supported by any other findings which might make one think of diabetes mellitus. The urine tests were all negative for sugar. As to the possibility of polyuria on the basis of diabetes mellitus, one would expect a certain amount of glycosuria. The lung findings are too vague to attribute any definite pathologic process to them; they are not substantiated by x-ray evidence of lung changes. The positive Homans sign does not necessarily mean thrombosis of the small veins in the calf. This is a finding which is frequently misinterpreted. Pain will be elicited with this test in instances of in-

FIGURE 2. Infarction and mural thrombus in apex of left auricle and mural thrombus in left ventricular wall.

flammation of the skin over the calf or of the subcutaneous tissues, or myositis of the muscles in this area, because the inflamed tissues are placed on stretch when one dorsiflexes the foot. The presence of considerable tenderness to pressure over this site would help to substantiate the view that there was some local inflammation of the tissues rather than a venous thrombosis. No statement was made as to whether or not there was an increase in the circumference of the calf at the involved site.

However, we cannot rule out the possibility that a venous thrombosis had occurred, with the lung findings being due to a small pulmonary embolism insufficient to be seen on x-ray or to produce symptoms. Disseminated non-necrotizing arteritis may be associated with venous thrombosis and with pulmonary embolism.

In my opinion the diagnosis which best fits the clinical picture and the course is some type of generalized vasculitis, with disseminated non-necrotizing arteritis the first choice, polyarteritis second, perhaps, and lupus last. One would expect to find the pathologic process in the peripheral arteries, at the bifurcation of the aorta, or in both iliacs (complete occlusion on the left side and incomplete on the right); involvement of the vascular tree in the kidney with secondary changes; a dilated, flabby heart with perhaps involvement of the coronary vessels in the process, and possibly signs of a small pulmonary infarct in the lower lung field.

Postmortem Examination

DR. WILLIAM BENNER: Gangrene of the left foot extended up onto the lower portion of the leg for about 10 cm. It was dry in type.

The heart was markedly enlarged, weighing 500 gm. The muscle was of good color but rather flabby and soft. On opening the heart, we did not find valvular lesions. However, a friable, polypoid mural thrombus was found in the apex of the left ventricle and a similar friable mural thrombus was found in the left ventricular wall just below the mitral ring (figure 2). All branches of the coronary arteries were remarkably smooth, and there was little, if any, evidence of atherosclerosis.

However, the posterior descending branch of the right coronary artery in its terminal portion entered an area of necrosis and infarction at the apex of the left ventricle. This infarcted area was directly under the first mural thrombus mentioned and was sharply demarcated; the maximum diameter was about 1½ cm. It did not extend through to the epicardium. There was no gross evidence of infarction on examining the external sur-

face. On opening the aorta, likewise, there was very little atherosclerotic involvement, but at the bifurcation there was a saddle embolus which showed evidence of varying degrees of age and of propagation both proximally and peripherally. More recent extension of the thrombus continued into both iliac arteries for about 8 cm., and the body or the head of the thrombus was propagating upward in the aorta about 2 cm.

QUESTION: Was there any canalization of the thrombus?

DR. BENNER: No. The embolus was partially adherent at the bifurcation, but the great part of it was not attached to the endothelium.

DR. ABRAMSON: Approximately how old would you say the embolic episode was?

DR. BENNER: The thrombus or the embolus, plus the addition of new blood and fibrin, was of varying age. It is rather difficult to state the specific number of days. However, there were adherence and early organization in the main portion of the embolus, indicating it had been there for some time, probably from the onset of the patient's symptoms (several weeks).

Both kidneys showed multiple areas of aseptic infarction, particularly the left, which was almost completely replaced by large, orange, infarcted areas (figure 3). These areas, likewise, showed varying ages. Some of them were raised—elevated from the kidney surface—indicating fairly recent origin, and some were somewhat depressed, indicating that some organization and retraction had begun.

FIGURE 3. Areas of aseptic infarction in left kidney.

A part of the saddle embolus at the bifurcation of the aorta was sectioned, and in a good portion of its circumference there was evidence of proliferation of fibroblasts and organization extending from the intimal surface of the aorta into the thrombus. The tails of this thrombus formation were more gelatinous and glistening and more friable, indicating more recent development. Likewise, at the head there was piling-up of fibrin, which was rather pale and also appeared to be of more recent origin. It was not attached to the intima, except right at the bifurcation. The two tails were both lying free in the iliac branches.

DR. ABRAMSON: How old was the infarction?

DR. BENNER: Probably several weeks old—at least three weeks. From three weeks on, it is very difficult to determine the age of an infarct. If it is completely fibrotic and replaced by scar tissue, it is several weeks old. Parts of this area at least could be five or six weeks old, which age would be compatible with the onset of the clinical symptoms. It could even be older than that.

Multiple sections of skeletal muscles and skin and subcutaneous tissue from the abdominal wall and the chest were examined with such diseases as polyarteritis and collagen disease in mind, but there was no evidence of these conditions. Sections of the aorta and iliac arteries did not reveal evidence of syphilis. The brain was not significantly abnormal. There was a slight amount of edema. There was no evidence of syphilis, grossly or microscopically.

Anatomic Diagnoses

1. Myocardial infarction and mural thrombus formation.
2. Saddle embolus, bifurcation of aorta, with gangrene of the left foot.
3. Multiple infarcts of the kidneys.
4. Chronic passive congestion of liver, lungs and spleen.

DR. K. J. COSTICH: We do not often have postmortem examinations of patients in this age group with this particular disease. I do not know how it compares with the clinical side, but from the experience of the Army it is not too common an occurrence. We had one case, that of an epileptic veteran, a laboratory technician, who, in the process of taking electrocardiograms, took several on himself and all were interpreted as normal. One evening while attending a picture show he suddenly became nauseated and went back to the ward; he died in about two hours. Necropsy showed that his coronary arteries had only pinpoint openings. He was 28 years old.

DR. LYLE A. BAKER: The formation of a subendocardial infarction brings out some very interesting problems. Most infarcts do start in the subendocardial layers of the myocardium, because the terminal coronaries leave the main vessels at right angles, penetrating deeply into the myocardium and through to the endocardium, and these small branches are not uncommonly occluded, leading to an infarct in the subendocardial region which would not go through to the surface. Such infarcts, of course, will cause the clinical syndrome of anginal pain and some degree of shock, and so forth, and they are a problem in clinical management in not a few cases. It is closely tied up with the term that Masters has made popular, that of coronary insufficiency versus actual myocardial infarction. The electrocardiograms in cases of subendocardial infarct do not have the characteristics of classic infarction, which involves the entire ventricular wall; the characteristics are identical with coronary insufficiency without infarction.

Clinically the problem is not so serious, as far as subendocardial infarct is concerned, because of the absence of a great many of the hazards of complete wall infarction such as rupture of the myocardium, formation of aneurysms, congestive failure, and so on. The danger in a case of subendocardial infarct is exactly what happened in this case—the formation of mural thrombi with embolization. Of course, that danger probably is as great in an insignificant subendocardial infarct as it is in a gross infarct involving the ventricular wall; in other words, the extent of mural thrombus formation is determined by the extent of area surface of the infarct in the subendocardial region, not by how far it extends through the wall to the epicardial surface.

That leads us, then, to the problem of myocardial infarction from the point of view of mural thrombus formation and embolization. There is no question that these patients should be kept at rest for a reasonable period. It probably need not be too long; in most cases two weeks or 15 days of bed rest probably are enough, but the indication for anticoagulant therapy is just as paramount as it would be if the patient had a gross infarct of the entire ventricular wall. We feel that anticoagulant therapy has definite value. In some 35 consecutive cases of myocardial infarction in which we have used anticoagulant therapy there has not been a gross embolic disturbance. We believe that anticoagulant therapy is definitely indicated in all cases of acute infarction. My own experience agrees pretty well with that of other workers over the country. Probably in the neighborhood of 20 to 25 per cent of all these patients have some complication from emboli during the convalescent period. So if you can prevent embolic phenomena, there is no doubt that you will lower the mortality and morbidity and probably improve the longevity of patients who have myocardial infarction.

Medicine's Expectations and Responsibilities in an Industrial Health Program

W. P. SHEPARD*

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W. P. SHEPARD

MEDICINE'S ultimate expectations and responsibilities in industrial health are to safeguard the health of the worker. As I outline the technics and benefits of preventive and curative medicine as applied in industry, suppose we imagine ourselves to be the workers. Then we can say, "These health services are for *me*!"

Environmental Control

First, let us consider the foundation of any industrial health program: a control of the working environment.[1] This broad term covers all conditions which make the place where men work as healthy and as safe as possible.

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Presented before the Pacific Northwest Industrial Health Conference at Portland, Oregon.

Toxic hazards—Heading the list of controllable working conditions are toxic and other hazards from dusts, fumes, chemicals, by-products and irradiation. Such hazards are comparatively rare, but they are, nevertheless, a major concern to industry because they are preventable and compensable. Medicine's responsibilities in this area are to make recommendations to management for the prevention of all known toxic hazards; to be alert to the potentialities of the constantly increasing number of new substances; to make sure that workers have the best possible diagnostic care and treatment for all injuries or illnesses incurred in connection with their work, and—most important—to protect the interests of both labor and management by complete impartiality in all compensable cases.

The purpose of workmen's compensation laws is to assure the worker fair treatment if he suffers an illness or injury resulting from or at work. But people have a natural tendency to blame any misfortune on their occupations. For example, the peculiar eye disease which was so troublesome in shipyards during World War II was attributed by workers to

all kinds of occupational factors: welding flashes, sawdust, excessive sunglare, and even pearl diving! The eye disease was found to be a virus infection as prevalent in one place as another, and it was stopped by ordinary epidemic control measures. Workers' injury and illness claims run the gamut from ridiculous through doubtful or possible causes to known work-connected disabilities. The physician alone has the heavy responsibility of evaluating claims and rendering an honest opinion.

Atmospheric and other conditions—Next on the list of environmental conditions which affect health in industry and which require control are lighting, ventilation, excessive noise, extremes of temperature and humidity, and exposure to radiant energy. Still considering yourselves to be industrial workers, have your eyes bothered you lately? How about asking your industrial physician to check the illumination at your desk? Are you worried about excessive noise deafening you and some of your fellow workers? Let the doctor or industrial hygienist check the number of decibels you are subjected to. Fifty per cent of us lose some hearing after we reach the age of 45. Have you a "hot-spot" in your plant? Have you ever heard of "thermature," the "effective temperature" which takes into account humidity as well as temperature? Let the experts check. You may find that your laundry or boiler room has a better "thermature" than the outdoors. Do you use x-ray in some process—perhaps to detect flaws in metal? Watch it! This is a delicate problem. Most metal engineers have no conception of the way that radiant energy bounces around a shield; nor do they realize, until some doctor finds that their bone marrow is failing to produce proper blood cells, that x-ray exposure is cumulative.

Control of infections—Our personal stake is also obvious in another aspect of industrial health—the control of infections, from the baffling problem of the common cold to such serious conditions as tuberculosis, anthrax and brucellosis. I know of a clerk with unrecognized tuberculosis who infected three other persons before her condition was discovered.

Accident prevention—The general field of environmental control also includes medical cooperation with the safety engineer. The worker who has more than one accident especially needs medical investigation. Whenever such a worker is helped to understand and correct his faulty work habits or the emotional or physical problems which make him an accident risk, we are all safer, not only in the plant, but on the road as well. The accident-repeater is primarily a medical problem. "Bad luck" rides his shoulder wherever he goes.

Preplacement Examinations

The second major area of medicine's responsibility in an industrial health program is medical advice on job placement through the preplacement physical examination.[1] I do not think it can be overemphasized that such examinations are an even greater advantage to the worker than to management. The applicant has more to lose—he may risk his life or his health in a job not suited to his physical abilities. Though it may seem cold-blooded, we might say that management risks only money. When preplacement physical examinations are carried out according to sound industrial health principles, they are used to determine what jobs an applicant *can* do—not to reject applicants because of certain physical defects. It is one of medicine's responsibilities in industrial health to insure that examination findings are not used to exclude anyone from work he can do without damage to his own health and safety or that of others.

Health Maintenance

The third important area in a sound industrial health program is general health maintenance.[1] Although occupational accidents and toxic hazards are important, they are relatively minor causes of absenteeism. The illnesses which cause most human and financial losses in industry are about the same as those occurring in any general population group; namely, respiratory diseases, digestive tract ailments, and other common conditions.

Periodic physical examinations—One of the most important instruments for general health maintenance is the periodic health examination for all employees. The frequency, type and comprehensiveness of these examinations

should be left to the physician. The examination will depend on varying factors—the hazards to which the worker is exposed, his age, medical history, and a complete review of his physical defects.

In the Metropolitan Life Insurance Company, we have found that there is no need for a complete physical examination on a stated date each year for every one of our more than 15,000 Home Office employees, the great majority of whom are young people. We make a careful and complete assay of their physical condition on employment. We know of their absences due to illnesses and what the doctor thought of their condition when they returned. We also know precisely what kind of work they are doing, how well or how poorly they are doing it, and what kind of supervision they get. We find that with this information, a skilled and specially trained interviewer (usually a nurse) can readily ascertain, at annual intervals, whether our younger employees have developed any health problems since last seen, and whether they need a special or complete examination by one of the doctors. Most employees do not. On the other hand, the older employees who are moving into the degenerative disease age bracket all see the doctor at least annually. Examination of these employees includes fluoroscopy of the chest and x-ray if necessary, an electrocardiogram, blood pressure reading, urinalysis and rectal examination, and, for women, pelvic examination for early detection of cancer. Special examinations, given when the doctor considers them necessary, include complete gastrointestinal x-ray studies, complete blood examination, and even a barium enema with x-ray.

Degenerative disease often can be detected in its earlier stages, when treatment is most effective. Frequently these examinations or interviews offer an opportunity to give good advice on work or living habits, recreation and health problems. When such advice is accepted, it can help workers avoid or postpone many run-of-the-mill disabilities.

First-aid and dispensary facilities—Good first-aid care and treatment of minor conditions which would not ordinarily require medical attention are important services which help minimize complications and lost time. Such services also contribute to understanding and good relations with workers, especially when management installs them of its own accord and takes an interest in their proper operation.

Medical follow-up—The industrial physician has a natural interest and, in workmen's compensation cases, a real responsibility for follow-up of employees who are under the care of their own doctors. Consultation with a good industrial physician is usually welcomed by local physicians when he inquires about a worker's health. Furthermore, the industrial physician often can help in rehabilitation by arranging a modification of the employee's duties when he first returns to work.

Health education—Health education is carried on, directly or indirectly, as a part of every other health service, but its effectiveness is greatly increased when it is developed into a well-balanced program that offers general health information and individual counseling to all workers. Experience at the Metropolitan with employees, policyholders and others indicates that information in booklets and advertisements is read and often heeded. Over the years, we have received a surprising number of reports crediting knowledge gained from such sources with saving lives and safeguarding health.

The services discussed are some of the essential aids which industrial medicine must be able to offer in the fields of environmental control, job placement and health maintenance in order to safeguard the health of the worker. They are equally important to every industry, regardless of its nature or size.[2]

Is there, for example, any difference between the need for protection of two or three employees in the rear of a small dry-cleaning shop from the toxic fumes of carbon tetrachloride, and controlling such fumes in a plant with 200 workers; for safeguarding the health of several butchers in a retail store, and preventing the spread of brucellosis among meat handlers in a big packing plant? Is there any difference between advising a garage owner to delegate the late hours to a helper, and advising the president of a large company to slow down? When we look at these services

from a personal, individual viewpoint, it is perfectly clear that *they are of equal importance to all industry regardless of the industry's size or nature.*

The most complete and systematic services naturally have been developed in larger, well-established industries. But such companies comprise only about 10 per cent of the nation's employers, and only one-fourth of its workers. The remaining three-fourths are employed in businesses too small to justify a full-time medical director. How, then, can smaller plants which employ the majority of the nation's workers obtain industrial health services?

Services for Small Plants

It is sometimes possible to arrange with a group of physicians who are especially interested in industrial medicine to serve several industries. Hours and pay are usually prorated according to payroll. This plan has worked out satisfactorily in many places and it has many advantages.[3] State and local medical societies usually have information about available plans of this type.

For the most part, smaller industries rely first on the part-time services of a local physician, who should have certain qualifications, and second on the services of an industrial nurse, full-time if possible, but if not, on her part-time services.

Part-time physicians in industry—In order to meet medicine's responsibilities in industrial health, the local physician chosen for part-time service in industry must have four essential qualifications:

First, of course, he must be a good doctor, a graduate of an accredited medical school, and he must be respected in the community.

Second, he must understand and have an interest in problems peculiar to industry. This means keeping regular hours in the plant, seeing employees who want advice, inspecting work places, and watching for potential hazards in new materials and procedures. It means accepting the responsibility as a physician to act as mediator between labor and management on health matters. It means willingness to learn new developments in industrial health by reading books and periodicals, and by attending meetings devoted to the subject. The industry should assist the physician to attend such meetings.

Third, the physician chosen must have a high sense of medical ethics and never use his industrial connections to build his private practice. He must respect and preserve existing good relationships between employees and their own doctors, and be able to work with physicians in the community as a respected colleague and consultant.

Fourth, he must have such status within the company that he can make health recommendations directly to top management. His medical and legal responsibilities alone make adequate status essential, but there are other considerations. The physician's position in the company indicates to workers the degree of importance management places in its health services. Also, physicians willing to devote time to industry are entitled to employee status which, as Newman[4] has pointed out, often gives them needed benefits of the company's retirement and disability plans.

Nursing service in industry—A full-time or, if necessary, a part-time industrial nurse can be an invaluable aid to workers, to management and to the industrial physician, but she, too, must meet certain requirements. The American Association of Industrial Nurses has available a list of recommended personal and professional qualifications for nurses in industry, as well as a resumé of recommended duties and responsibilities.[5]

An industrial nurse must be, first, a good nurse, a graduate of an accredited school of nursing. She must have a well-developed interest in people and the ability to work with all types. She must have good judgment and be able to maintain a balance between her responsibilities to management and to the individual worker.

Ready access to medical supervision is a necessity. Nurses working in small plants without full-time medical supervision are sometimes asked by employers and employees to treat illness and injury to an extent which is dangerous and often illegal. The worker and management as well as the nurse are protected when she has a set of standing orders

signed by the plant physician. The amount and kind of emergency care and treatment a nurse may give is dependent on a physician's legal order. Verbal instructions have no place where legal liability is a factor.

Although part-time medical and nursing services may offer more problems than a complete, full-time program, they can be adequate for the needs of small plants. Properly developed, they provide for management and worker the same essential protection afforded by the full-time programs of larger plants. The responsibilities of an industrial health team, regardless of the size or nature of the industry it serves, are:

1. To protect employee and employer alike from hazards arising from and in the course of employment.
2. To bring to the industry every known means in preventive and curative medicine which may improve the health of all the workers, including management.
3. To adjust the health program to the overall objectives of the industry, with due regard for economy and efficiency, as well as the known health needs of the employees.
4. To advise both management and labor on all policies having a health aspect. These range from job placement to the medical care included in fringe benefits.
5. To act as a bridge between the industry and the community health and welfare agencies so that employees and their families may take full advantage of community facilities available to them.

Cost and Profit

Management must naturally know two things about an industrial health program: What does it cost and what do we get? I have tried to explain what management gets. The cost will run from $5 to $30-plus per employee-year, depending on how complete the program is. The latter figure should provide almost complete medical and hospital care for the majority of illnesses. Most of the preventive services mentioned can be provided on a $12 to $15 per employee per year budget.

Whether such a program will pay for itself or even save money, many physicians are loath to say. Some companies writing workmen's compensation insurance can show a saving in claims that is more than enough to pay for the program.

There is much that is intangible about health and medical service, as is true with all employer-employee relations. Very few industries have discontinued a health program once it has been started. The benefits, both preventive and curative, should be self-evident. If greater profits result, as they can, they should be considered a fortunate by-product.

Conclusion

What medicine expects from a successful industrial health program is exactly what both management and labor want, too—healthier, happier, more productive workers, and a more prosperous industry. As more physicians and nurses develop the skills needed for effective industrial health services, and as more industries offer opportunities to use these skills, medicine's expectations—which we all share—can become realities.

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Editorials

Postgraduate Medicine

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WHAT ABOUT THE LIPIDS?

FAT is much in the scientific news. If life insurance statistics as to the abbreviated longevity of the overweight seem alarming, let us remember that the warning is not recent. In the aphorisms of Hippocrates, written about 400 B.C., appears: "Fat men are more likely to die suddenly than the slender." Once fat was just fat, as protein was only protein, but now the variety of the lipids and their structural differences are known to be well-nigh as complex as those of the proteins. The exact significance of these chemical differences still perplexes pharmacologists, physiologists and physicians generally.

Gradually many facts are being assembled relating to the biologic aspects of fat, and some day an orderly system may come from the puzzling picture that now prevails. The impression is strong that high fat diets and high levels of cholesterol are related to arteriosclerosis and coronary thrombosis. Dr. Bronte-Stewart[1] of Cape Town has found that the nature of the dietary fat may be a factor in determining the content of lipid in serum. Unsaturated fatty acids depress the level of cholesterol in serum. The Cape Town investigators demonstrated that eating butter, beef drippings and large amounts of eggs was followed by an increase in the β-lipoprotein of the plasma; olive, sunflower seed, ground-nut or seal oils were associated with low levels of serum β-lipoproteins. On this observation the London *Lancet* comments:

> Food fats and oils thus seem to fall into two classes, whose effects on plasma-lipids are antagonistic to each other. If these results are substantiated, coronary-artery disease becomes in part a preventable disorder—but at the cost of a complete revolution in our present-day dietary habits. The hydrogenation plants of our modern food industry may turn out to have contributed to the causation of a major disease. To preserve the unsaturated fatty acids in vegetable oils and marine oils, and to make these oils palatable and acceptable to industrial populations would be a herculean task for those who would seek to change people's eating habits. All the principles of the modern

margarine industry might have to be put into reverse.

The adaptation of this knowledge to current dietary practice is a concern of ethnologists, sociologists and statesmen as well as the scientists. Succinctly the *Lancet*[2] states: "In this type of research the unit of time is the decade. For the most part physiologists are still preoccupied by what happens in a few milliseconds and even experimental pathologists like to get their results in a few weeks."

The answers to the problems that confront investigators in dietary mechanisms are not easily reached. Ancel Keys emphasizes that knowledge of the ratio of essential to total fatty acids is not nearly complete for any one artificial dietary fat. Obviously, evidence must be accumulated on the dietary intake of varieties of fat by great numbers of people over many years, and this in turn related to the degenerative diseases that they manifest. I can remember a discussion of this difficulty with Professor Lafayette Mendel over 30 years ago. He was inclined to despair that such investigations would ever be successful on humans.

In its mid-century survey of medical research, the American Foundation[3] lists some of the evidence supporting the part played by cholesterol in atherosclerosis:

1. Cholesterol is regularly found in atheromatous deposits.

2. Excessive dietary cholesterol produces a high serum cholesterol concentration and atherosclerosis in rabbits and chickens.

3. Average concentrations of serum cholesterol are higher in persons with coronary occlusion than in normal persons of the same age groups.

Nevertheless, the American Foundation indicates many investigators feel that preoccupation with cholesterol has greatly and harmfully narrowed the investigative picture:

1. The concentrations and proportions of lipids in the serum may be as significant as cholesterol.

2. Rabbits have mechanisms different from those of humans and are remarkably sensitive to dietary cholesterol.

3. In man, excess dietary cholesterol is without effect on blood cholesterol concentrations if calorie and fat intakes are constant.

4. Arterial susceptibility to lipid deposition is not constant or consistent.

5. Apparently, degenerative processes or local injuries influence deposit of cholesterol in the walls of arteries.

All this leads to the conclusion that "so long as the mechanisms by which the 'noxious influences' that injure arterial tissues and make them susceptible to lipid deposition remain unknown, the problem of atherosclerosis cannot be completely solved."

Still further complicating an understanding of arteriosclerosis are the influences of hormones on cholesterol metabolism, as well as diet, obesity, constitutional conditions such as diabetes, and various lipotropic substances. Studies made at Minnesota, Oxford and Naples have not produced evidence to correlate obesity with high cholesterol levels. The clinical use of various lipotropic substances such as choline, methionine and betaine has led to contradictory results. There seems to be no firm scientific basis for the widespread clinical use of such preparations in either preventing or treating arteriosclerosis.

Fortunately, new technics involving both chemical and physical methods are being developed constantly, yielding more and more intimate knowledge of how various substances taken into the body reach their ultimate destinations and the changes that take place in them during such processes. Studies of the tissues of the blood vessels, the metabolism of the steroids and other lipids, and the physical study of the lipids in the blood are disclosing basic information which may ultimately lead to an understanding of the degenerative processes that result in such death-producing incidents as cerebral hemorrhage, coronary thrombosis, and hypertension.

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HERPES VIRUS

APPARENTLY 90 per cent of people over 15 years of age have in their blood specific antibodies against the virus of herpes. Reginald T. Brain[1] of the famous Royal Free Hospital and the Hospital for Sick Children of Great Ormond Street, London, says that the virus of herpes simplex is so widespread that few members of the human race avoid some passing acquaintance with it. The latent virus becomes activated in response to such stimuli as febrile illness, menstruation and irritation of or damage to the skin, mucous membranes or sensory nerves. Immediately small vesicles appear on an inflammatory base, perhaps become confluent, and are accompanied by tenderness and enlargement of the regional lymph nodes. Among the most severe of the lesions are the recurrent herpes which attack the conjunctiva and the cornea. These are the commonest ocular complications of malaria.

The herpes virus once loose in the human body is ubiquitous. Among herpetic lesions observed and discussed by Dr. Brain are cases of trigeminal neuralgia associated with herpes simplex, primary herpetic gingivostomatitis, and primary herpetic infections of the genitals, eye and skin. In infants lacking in immunity to the virus many organs and tissues may be attacked, but the most serious consequences occur when the liver, the suprarenal glands or the central nervous system is involved. The relationship of the virus to hepatitis and encephalitis has been established. Nurses and other attendants caring for infants during outbreaks of epidemic varicelliform eruptions have developed contact lesions on the hands and forearms. The vaccinia virus may produce eruptions which are difficult to distinguish from those caused by the virus of herpes.

In 1919 Lowenstein produced infections in the cornea of a rabbit with virus from human herpes simplex, and reported that Grüter had done similar experiments in 1912. Dr. T. F. McNair Scott[2] says that circulating antiherpetic antibodies are found in up to 93 per cent of persons in the lower income brackets but in only 37 per cent of those in high income brackets. Infants under six months of age are extremely susceptible but develop resistance with age. Apparently the condition is more frequently spread by contact than as an air-borne infection. The facts that the virus may exist in a latent state in almost all people, that the incubation period for infection is short, and that there is a lack of any specific method of control or treatment contribute to the difficulty of overcoming this condition. The clinical manifestations are fortunately self-limited. Measures are necessary to prevent secondary bacterial infection. Dr. Scott recommends for ordinary skin vesicles the application of ZEPHIRAN® chloride 1:1000 or any other antiseptic drying agent. When the virus of herpes attacks the eye, the attention of specialists is demanded for the application of forms of local treatment which they think desirable.

At the annual congress of the Ophthalmological Society of the United Kingdom, held in London in April 1956, Mr. A. J. B. Goldsmith[3] reviewed the ocular manifestations of the two herpes viruses only recently identified. In the treatment of dendriform ulcers he said that chemical destruction of the corneal epithelium still seemed to be the only effective method of eliminating the virus. Topical cortisone was considered to be positively dangerous in the early stages and antibiotic or chemotherapeutic agents were ineffective.

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HISTORY OF MEDICINE

A SURVEY of American and Canadian medical schools in 1951 showed that 37 American and seven Canadian medical schools had some provisions for teaching the history of medicine. In 17 schools in the United States and in five in Canada there were organized departments or divisions of the history of medicine;

otherwise, the courses were rather indiscriminate and varied from a few lectures to a series of co-ordinated lectures. In most instances, however, medical colleges have treated the history of medicine as a rather despised stepchild. True, many distinguished teachers regularly refer to the history of their subjects in didactic courses, but such courses are becoming less frequent because bedside instruction is dominant.

In a recent survey, Dr. Ilza Veith,[1] assistant professor of the history of medicine at the University of Chicago, notes that medical history has value not only as a cultural subject but also for its contribution to medical progress. Such significant medicaments as quinine, cocaine, ephedrine and Rauwolfia serpentina have been added to the modern pharmacopeia from knowledge acquired by the reading of old documents.

Recently, medical history has abandoned emphasis on names, dates and anecdotes and has begun to fit itself into the cultural scheme of education with special relationship to such disciplines as sociology, economics, ethnology and history. This relationship is emphasized by the increased attention now given to the social aspects of medical science.

Dr. Veith calls attention also to the cultural aspects of education in the history of medicine. Great writers of the past who became the heroes of medicine impress even modern readers with the beauty of their style and their clarity of expression in discussing the most scientific of medical subjects.

For the most part, medical history is taught not by trained historians but by physicians who have a special interest in this subject. Fortunately, their enthusiasm stimulates medical students to become interested in the narration of the continuity of medical knowledge from the earliest times to the present.

Dr. Veith ends her inspirational article with a quotation from Dr. James B. Herrick, who was not only a great clinician but more than an amateur in medical history. He recognized that the history of medicine leads to a better understanding of present medical knowledge. It teaches the student the importance of going for information to original articles and, above all, it leads him to medical biographies. Thus, he acquires a reverence for the ethics and traditions of medicine which are characteristic of the truly great physician.

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EVALUATING QUALITY IN HOSPITALS

The quality of medical care in hospitals," says E. M. Bluestone, "counts more than the quantity." He is convinced that there is no substitute for a personal tour of inspection and perhaps "you cannot really know a hospital until you have personally sampled its wares." In an appendix in a book by Alden B. Mills called "Hospital Public Relations," Dr. Bluestone lists 100 criteria that may be utilized in determining the quality of medical care in hospitals. They deal with the functions of the governing board, the physical facilities, the policies, the administration, the staff, and the care of patients. Many of these criteria are often overlooked by those who concern themselves with hospitals. How many investigate the extent, importance and honesty of the scientific output of hospitals? Who gives thought to the effects of such words used around hospitals as "incurable," "charity," "indigent," "cancer," or those hushed abbreviations which most intelligent patients now understand as "Ca," "D. and C.," or "V.D."? How many think of the extent to which hospitals depreciate the quality of medical service by indulging themselves as corporations in medical practice? What is the quality of social, financial and vital statistics and to what uses are they put? Dr. Bluestone's 100 criteria are stimulators of thought and deterrents to careless obliviousness.

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